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| NEWS 2 | JAN 02 | STN pricing information for 2008 now available |
| NEWS 3 | JAN 16 | CAS patent coverage enhanced to include exemplified prophetic substances |
| NEWS 4 | JAN 28 | USPATFULL, USPAT2, and USPATOLD enhanced with new custom IPC display formats |
| NEWS 5 | JAN 28 | MARPAT searching enhanced |
| NEWS 6 | JAN 28 | USGENE now provides USPTO sequence data within 3 days of publication |
| NEWS 7 | JAN 28 | TOXCENTER enhanced with reloaded MEDLINE segment |
| NEWS 8 | JAN 28 | MEDLINE and LMEDLINE reloaded with enhancements |
| NEWS 9 | FEB 08 | STN Express, Version 8.3, now available |
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| NEWS 11 | FEB 25 | IFIREF reloaded with enhancements |
| NEWS 12 | FEB 25 | IMSPRODUCT reloaded with enhancements |
| NEWS 13 | FEB 29 | WPINDEX/WPIDS/WPIX enhanced with ECLA and current U.S. National Patent Classification |
| NEWS 14 | MAR 31 | IFICDB, IFIPAT, and IFIUDB enhanced with new custom IPC display formats |
| NEWS 15 | MAR 31 | CAS REGISTRY enhanced with additional experimental spectra |
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| NEWS 18 | MAR 31 | EMBASE, EMBAL, and LEMBASE reloaded with enhancements |
| NEWS 19 | APR 04 | STN AnaVist, Version 1, to be discontinued |
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| NEWS 22 | APR 28 | IMSRESEARCH reloaded with enhancements |
| NEWS 23 | MAY 30 | INPAFAMDB now available on STN for patent family searching |
| NEWS 24 | MAY 30 | DGENE, PCTGEN, and USGENE enhanced with new homology sequence search option |
| NEWS 25 | JUN 06 | EPFULL enhanced with 260,000 English abstracts |
| NEWS 26 | JUN 06 | KOREAPAT updated with 41,000 documents |
| NEWS 27 | JUN 13 | USPATFULL and USPAT2 updated with 11-character patent numbers for U.S. applications |
| NEWS 28 | JUN 19 | CAS REGISTRY includes selected substances from web-based collections |
| NEWS 29 | JUN 25 | CA/CAplus and USPAT databases updated with IPC reclassification data |

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NEWS 33 JUN 30 STN AnaVist enhanced with database content from EPFULL

NEWS EXPRESS JUNE 27 08 CURRENT WINDOWS VERSION IS V8.3, AND CURRENT DISCOVER FILE IS DATED 23 JUNE 2008.

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* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 17:23:25 ON 25 JUL 2008

=> FILE REG

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 0.21 | 0.21 |

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DICTIONARY FILE UPDATES: 24 JUL 2008 HIGHEST RN 1035921-65-3

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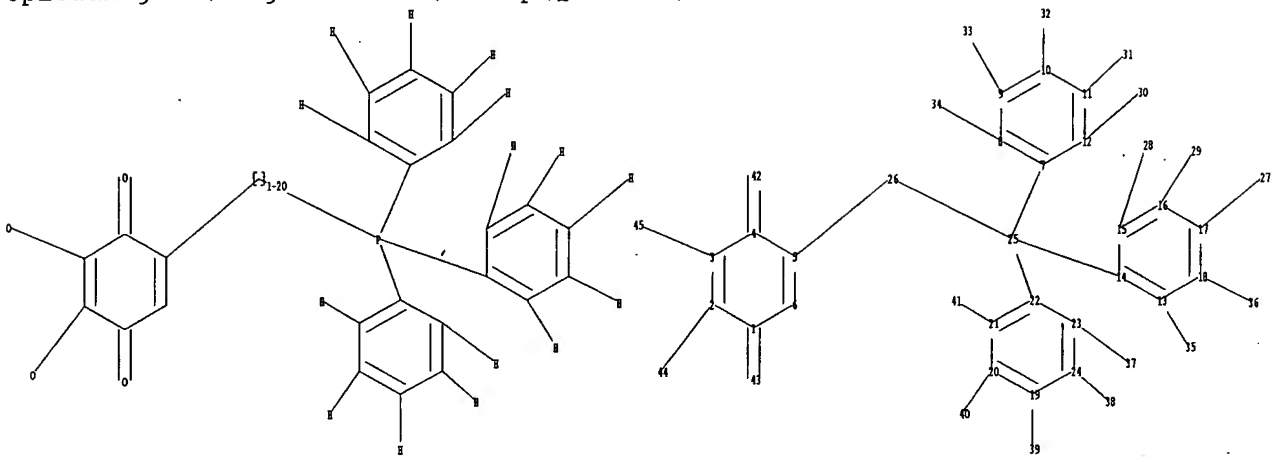

chain nodes :
25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
24
chain bonds :
1-43 2-44 3-45 4-42 5-26 7-25 8-34 9-33 10-32 11-31 12-30 13-35 14-25
15-28 16-29 17-27 18-36 19-39 20-40 21-41 22-25 23-37 24-38 25-26
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12 13-14 13-18
14-15 15-16 16-17 17-18 19-20 19-24 20-21 21-22 22-23 23-24
exact/norm bonds :
1-2 1-6 1-43 2-3 2-44 3-4 3-45 4-5 4-42 5-6
exact bonds :
5-26 7-25 8-34 9-33 10-32 11-31 12-30 13-35 14-25 15-28 16-29 17-27
18-36 19-39 20-40 21-41 22-25 23-37 24-38 25-26
normalized bonds :
7-8 7-12 8-9 9-10 10-11 11-12 13-14 13-18 14-15 15-16 16-17 17-18 19-20
19-24 20-21 21-22 22-23 23-24

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom
20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:CLASS 26:CLASS 27:CLASS 28:CLASS
29:CLASS 30:CLASS 31:CLASS 32:CLASS 33:CLASS 34:CLASS 35:CLASS 36:CLASS
37:CLASS 38:CLASS 39:CLASS 40:CLASS 41:CLASS 42:CLASS 43:CLASS 44:CLASS
45:CLASS

L1 STRUCTURE UPLOADED

=> S L1 FULL
FULL SEARCH INITIATED 17:24:10 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 142 TO ITERATE

100.0% PROCESSED 142 ITERATIONS 21 ANSWERS
SEARCH TIME: 00.00.01

L2 21 SEA SSS FUL L1

=> FILE CAPLUS

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 178.36 | 178.57 |

FILE 'CAPLUS' ENTERED AT 17:24:21 ON 25 JUL 2008


FILE COVERS 1907 - 25 Jul 2008 VOL 149 ISS 5
FILE LAST UPDATED: 24 Jul 2008 (20080724/ED)

Caplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2008.

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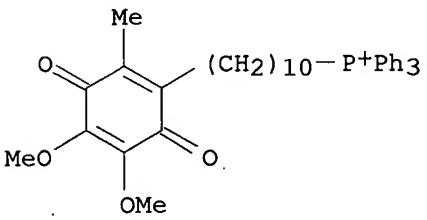
=> S L2
L3 35 L2

=> S L3 AND ANTIOXIDANT
133228 ANTIOXIDANT
L4 28 L3 AND ANTIOXIDANT

=> D L4 IBIB ABS HITSTR 1-28

L4 ANSWER 1 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2008:459952 CAPLUS
DOCUMENT NUMBER: 149:47117
TITLE: Rapid and extensive uptake and activation of hydrophobic triphenylphosphonium cations within cells
AUTHOR(S): Ross, Meredith F.; Prime, Tracy A.; Abakumova, Irina; James, Andrew M.; Porteous, Carolyn M.; Smith, Robin

A. J.; Murphy, Michael P.
CORPORATE SOURCE: Wellcome Trust/MRC Building, Medical Research Council Dunn Human Nutrition Unit, Cambridge, CB2 0XY, UK
SOURCE: Biochemical Journal (2008), 411(3), 633-645
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mitochondria-targeted mols. comprising the lipophilic TPP (triphenylphosphonium) cation covalently linked to a hydrophobic bioactive moiety are used to modify and probe mitochondria in cells and in vivo. However, it is unclear how hydrophobicity affects the rate and extent of their uptake into mitochondria within cells, making it difficult to interpret expts. because their intracellular concentration in different compartments is uncertain. To address this issue, we compared the uptake into both isolated mitochondria and mitochondria within cells of two hydrophobic TPP derivs., [3H]MitoQ (mitoquinone) and [3H]DecylTPP, with the more hydrophilic TPP cation [3H]TPMP (methyltriphenylphosphonium). Uptake of MitoQ by mitochondria and cells was described by the Nernst equation and was .apprx.5-fold greater than that for TPMP, as a result of its greater binding within the mitochondrial matrix. DecylTPP was also taken up extensively by cells, indicating that increased hydrophobicity enhanced uptake. Both MitoQ and DecylTPP were taken up very rapidly into cells, reaching a steady state within 15 min, compared with .apprx.8 h for TPMP. This far faster uptake was the result of the increased rate of passage of hydrophobic TPP mols. through the plasma membrane. Within cells MitoQ was predominantly located within mitochondria, where it was rapidly reduced to the ubiquinol form, consistent with its protective effects in cells and in vivo being due to the ubiquinol antioxidant. The strong influence of hydrophobicity on TPP cation uptake into mitochondria within cells facilitates the rational design of mitochondria-targeted compds. to report on and modify mitochondrial function in vivo.
IT 444890-41-9, Mitoquinone
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(rapid and extensive uptake and activation of hydrophobic triphenylphosphonium cations within cells)
RN 444890-41-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)




REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2008:164099 CAPLUS
DOCUMENT NUMBER: 148:206611

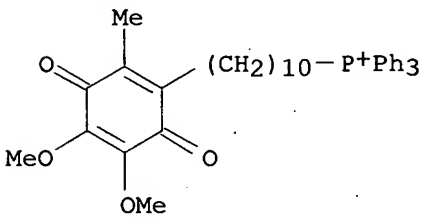
TITLE: Methods for reducing anthracycline-induced toxicity
INVENTOR(S): Kalyanaraman, Balaraman; Kalivendi, Shasi Vardhan; Joseph, Joy
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 21pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| US 20080032940 | A1 | 20080207 | US 2007-834799 | | 20070807 |
| PRIORITY APPLN. INFO.: | | | US 2006-836247P | P | 20060807 |

AB Methods for treating cancers/tumors include administering to a subject an effective amount of a mitochondria-targeted antioxidant alone or in combination with a chemotherapeutic agents. Likewise, methods for mitigating toxicity associated with a chemotherapeutic agent include administering an effective amount of a mitochondria-targeted antioxidant with a single or with multiple chemotherapeutic agents. The invention relates more particularly to coadministering a mitochondria-targeted antioxidant with a chemotherapeutic agent to attenuate the agent's toxicity to normal cells and to enhance its toxicity to tumor cells. At low micromolar concns., mitochondria-targeted antioxidant MitoQ differentially affected normal cells and tumor cells. MitoQ syngerized with doxorubicin (DOX) to enhance caspase-3 activity in tumor cell lines (MCF-7, MCF-10A and SH-SY5Y), but not in normal cells lines (CM and 1-19c2). In fact, MitoQ attenuated DOX-induced caspase-3 activity in normal cell lines.

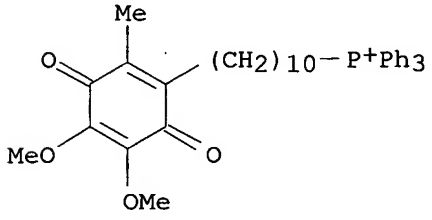
IT 444890-41-9P, MitoQ
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(as mitochondria-targeted antioxidant; reducing anthracycline-induced toxicity by coadministering mitochondria-targeted antioxidant)

RN 444890-41-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)




IT 336184-91-9
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as mitochondria-targeted antioxidant; reducing anthracycline-induced toxicity by coadministering mitochondria-targeted antioxidant)

RN 336184-91-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



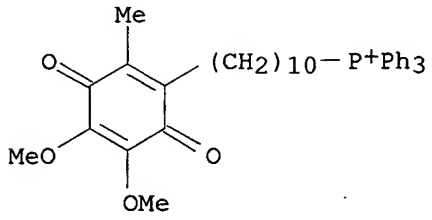

● $Br^-$

L4 ANSWER 3 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2008:62861 CAPLUS
DOCUMENT NUMBER: 148:182855
TITLE: Is Antioxidant Potential of the Mitochondrial Targeted Ubiquinone Derivative MitoQ Conserved in Cells Lacking mtDNA?
AUTHOR(S): Lu, Chao; Zhang, Dawei; Whiteman, Matthew; Armstrong, Jeffrey S.
CORPORATE SOURCE: Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
SOURCE: Antioxidants & Redox Signaling (2008), 10(3), 651-660
CODEN: ARSIF2; ISSN: 1523-0864
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB MitoQ was developed as a mitochondrial targeted antioxidant for diseases associated with oxidative stress. Here we show that MitoQ blocks the generation of reactive oxygen species (ROS) and mitochondrial protein thiol oxidation, and preserves mitochondrial function and ultrastructure after glutathione (GSH) depletion. Furthermore, the antioxidant effect of MitoQ is conserved in cells lacking mitochondrial DNA, indicating that its antioxidant properties do not depend on a functional electron transport chain (ETC). Our results elucidate the antioxidant mechanism of MitoQ and suggest that it may be a useful therapeutic for disorders associated with a dysfunctional ETC and increased ROS production

IT 444890-41-9, MitoQ
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MitoQ antioxidant effect via blocking ROS and protein thiol oxidation, and preserving mitochondria independently of glutathione and electron transport chain)

RN 444890-41-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)




REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:1220757 CAPLUS
DOCUMENT NUMBER: 148:2715
TITLE: Mitochondrial redox cycling of mitoquinone leads to superoxide production and cellular apoptosis
AUTHOR(S): Doughan, Abdulrahman K.; Dikalov, Sergey I.
CORPORATE SOURCE: Free Radical in Medicine Core, Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA
SOURCE: Antioxidants & Redox Signaling (2007), 9(11), 1825-1836
CODEN: ARSIF2; ISSN: 1523-0864
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

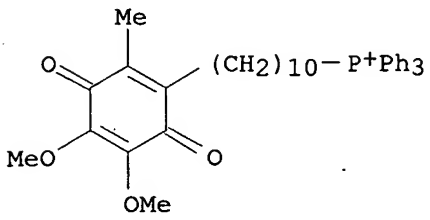
AB The mitochondria-targeted drug mitoquinone (MitoQ) has been used as an antioxidant that may selectively block mitochondrial oxidative damage; however, it has been recently suggested to increase reactive oxygen species (ROS) generation in malate- and glutamate-fueled mitochondria. To address this controversy, we studied the effects of MitoQ on endothelial and mitochondrial ROS production We found that in a cell-free system with flavin-containing enzyme cytochrome P 450 reductase, MitoQ is a very efficient redox cycling agent and produced more superoxide compared with equal concns. of menadione (10-1000 nM). Treatment of endothelial cells with MitoQ resulted in a dramatic increase in superoxide production In isolated mitochondria, MitoQ increased complex I-driven mitochondrial ROS production, whereas supplementation with ubiquinone-10 had no effect on ROS production Similar results were observed in mitochondria isolated from endothelial cells incubated for 1 h with MitoQ. Inhibitor anal. suggested that the redox cycling of MitoQ occurred at two sites on complex I, proximal and distal to the rotenone-binding site. This was confirmed by demonstrating the redox cycling of MitoQ on purified mitochondrial complex I as well as NADH-fueled submitochondrial particles. Mitoquinone time- and dose-dependently increased endothelial cell apoptosis. These findings demonstrate that MitoQ may be prooxidant and proapoptotic because its quinone group can participate in redox cycling and superoxide production In light of these results, studies using mitoquinone as an antioxidant should be interpreted with caution.

IT 845959-50-4
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mitochondrial redox cycling of mitoquinone leads to superoxide production and cellular apoptosis)
RN 845959-50-4 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-

yl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

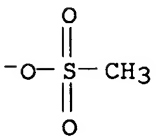
CM 1

CRN 444890-41-9
CMF C37 H44 O4 P



CM 2

CRN 16053-58-0
CMF C H3 O3 S



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

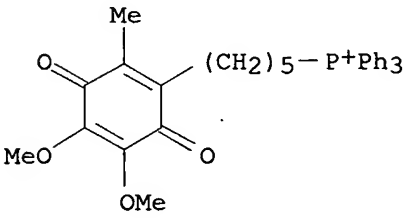
L4 ANSWER 5 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:965666 CAPLUS
DOCUMENT NUMBER: 148:135860
TITLE: Mitochondria-targeted antioxidants do not prevent tumor necrosis factor-induced necrosis of L929 cells
AUTHOR(S): Jarvis, Reagan M.; Goettert, Jana; Murphy, Michael P.; Ledgerwood, Elizabeth C.
CORPORATE SOURCE: Department of Biochemistry, University of Otago, Dunedin, N. Z.
SOURCE: Free Radical Research (2007), 41(9), 1041-1046
CODEN: FRARER; ISSN: 1071-5762
PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mitochondrial production of reactive oxygen species (ROS) is widely reported as a central effector during TNF-induced necrosis. The effect of a family of mitochondria-targeted antioxidants on TNF-induced necrosis of L929 cells was studied. While the commonly used lipid-soluble antioxidant BHA effectively protected cells from TNF-induced necrosis, the mitochondria-targeted antioxidants MitoQ3, MitoQ5, MitoQ10 and MitoPBN had no effect on TNF-induced necrosis. Since BHA also acts as an uncoupler of mitochondrial membrane potential, two addnl. uncouplers were tested. FCCP and CCCP both provided dose-dependent inhibition of TNF-induced necrosis.

In conclusion, the generation of mitochondrial ROS may not be necessary for TNF-induced necrosis. Instead, these results suggest alternative mitochondrial functions, such as a respiration-dependent process, are critical for necrotic death.

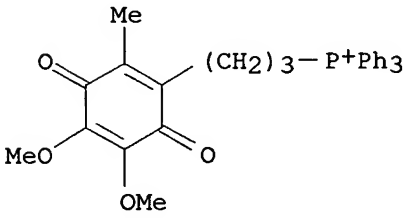
IT 764723-90-2 845959-57-1
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mitochondria-targeted antioxidants do not prevent tumor necrosis factor-induced necrosis of L929 cells)

RN 764723-90-2 CAPLUS
CN Phosphonium, [5-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentyl]triphenyl-, iodide (1:1) (CA INDEX NAME)




● $I^-$

RN 845959-57-1 CAPLUS
CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl-, bromide (1:1) (CA INDEX NAME)




● $Br^-$

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:922908 CAPLUS
DOCUMENT NUMBER: 147:356077
TITLE: Targeting antioxidants to mitochondria and cardiovascular diseases: the effects of mitoquinone
AUTHOR(S): Rocha, Milagros; Victor, Victor Manuel
CORPORATE SOURCE: Department of Pharmacology, Faculty of Medicine, Universitat of Valencia, Valencia, Spain

SOURCE: Medical Science Monitor (2007), 13(7), RA132-RA145
CODEN: MSMOFR; ISSN: 1234-1010
PUBLISHER: International Scientific Literature, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Mitochondria have long been known to play a critical role in maintaining the bioenergetic status of cells under physiol. conditions. Mitochondria produce large amts. of free radicals, and mitochondrial oxidative damage can contribute to a range of degenerative conditions including cardiovascular diseases (CVDs). Although the mol. mechanisms responsible for mitochondrion-mediated disease processes are not correctly understood, oxidative stress seems to play an important role. Consequently, the selective inhibition of mitochondrial oxidative damage is an obvious therapeutic strategy. This review considers the process of CVD from a mitochondrial perspective and provides a summary of the following areas: reactive oxygen species (ROS) production and its role in pathophysiol. processes such as CVD, currently available antioxidants and possible reasons for their efficacy and inefficacy in ameliorating oxidative stress-mediated diseases, and recent developments in mitochondria-targeted antioxidants that concentrate on the matrix-facing surface of the inner mitochondrial membrane. These mitochondrion-targeted antioxidants have been developed by conjugating the lipophilic triphenylphosphonium cation to antioxidant moieties such as ubiquinol. These compds. pass easily through biol. membranes and, due to their pos. charge, they accumulate several-hundred-fold within mitochondria. In this way they protect against mitochondrial oxidative damage and show potential as a future therapy for CVDs.

IT 845959-50-4, Mitoquinone
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(loss of control of reactive oxygen species formation in mitochondria leads to pathol. of cardiovascular disease in animals and mitoquinone protect against mitochondrial oxidative damage and showed potential as future therapy for CVD)

RN 845959-50-4 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 444890-41-9
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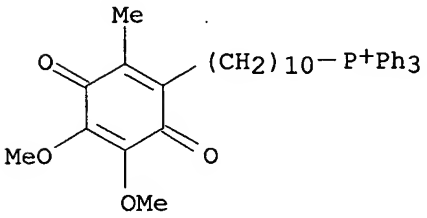
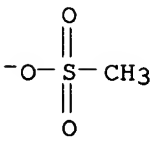


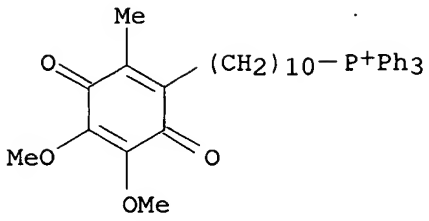

CM 2

CRN 16053-58-0
CMF C H3 O3 S



REFERENCE COUNT: 126 THERE ARE 126 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:818711 CAPLUS
DOCUMENT NUMBER: 147:335184
TITLE: Drug evaluation: MitoQ - a mitochondrial-targeted antioxidant
AUTHOR(S): Tauskela, Joseph S.
CORPORATE SOURCE: Institute for Biological Sciences, Synaptic Pathophysiology Group, National Research Council, Ottawa, ON, K1A 0R6, Can.
SOURCE: IDrugs (2007), 10(6), 399-412
CODEN: IDRUFN; ISSN: 1369-7056
PUBLISHER: Thomson Scientific
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. MitoQ is an orally active antioxidant that has the ability to target mitochondrial dysfunction. The agent is currently under development by Antipodean Pharmaceuticals Inc and is in phase II clin. trials for Parkinson's disease and liver damage associated with HCV infection. MitoQ demonstrated encouraging preclin. results in numerous studies in isolated mitochondria, cells and tissues undergoing oxidative stress and apoptotic death. The aim of MitoQ is to not only mimic the role of the endogenous mitochondrial antioxidant coenzyme Q10 (CoQ10), but also to substantially augment the antioxidant capacity of the coenzyme to supraphysiol. levels in a mitochondrial membrane potential-dependent manner. MitoQ represents the first foray into the clinic of an attempt to deliver an antioxidant to an intracellular region that is responsible for the formation of increased levels of potentially deleterious reactive oxygen species. Results from the clin. trials with MitoQ will have important repercussions regarding the relevance of a mitochondria-targeted approach.
IT 444890-41-9, MitoQ
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mitochondrial-targeted antioxidant MitoQ)
RN 444890-41-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)

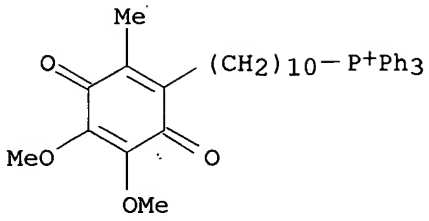


REFERENCE COUNT: 91 THERE ARE 91 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:739270 CAPLUS
DOCUMENT NUMBER: 147:273456
TITLE: Quantitation and metabolism of mitoquinone, a mitochondria-targeted antioxidant, in rat by liquid chromatography/tandem mass spectrometry
AUTHOR(S): Li, Yan; Zhang, Hu; Fawcett, J. Paul; Tucker, Ian G.
CORPORATE SOURCE: School of Pharmacy, University of Otago, Dunedin, N. Z.
SOURCE: Rapid Communications in Mass Spectrometry (2007), 21(13), 1958-1964
CODEN: RCMSEF; ISSN: 0951-4198
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mitoquinone (MitoQ10 mesylate) is a mitochondria-targeted antioxidant undergoing development for the treatment of neurodegenerative diseases. The aim of this study was to develop and validate an assay based on liquid chromatog./tandem mass spectrometry (LC/MS/MS) to determine mitoquinone and to detect and identify the metabolites of MitoQ10 in rat plasma after an oral dose. After a simple protein precipitation step, plasma samples were analyzed by reversed-phase liquid chromatog. using gradient elution with acetonitrile/water/formic acid. Electrospray ionization in the pos. ion mode with multiple reaction monitoring (MRM) was used to analyze mitoquinone employing the deuterated compound (d3-MitoQ10 mesylate) as internal standard The calibration curve for mitoquinone was linear over the concentration range 0.5-250 ng/mL with a correlation coefficient >0.995. The method was sensitive (limit of quantitation 0.5 ng/mL) and had acceptable accuracy (relative error <8.7%) and precision (intra- and inter-day coefficient of variation <12.4%). Recoveries of mitoquinone at concns. of 1.5, 20 and 200 ng/mL were in the range 87-114%. The method was successfully applied to a pharmacokinetic study in rat after a single oral dose in which four metabolites of MitoQ10 were tentatively identified as hydroxylated MitoQ10, desmethyl MitoQ10 and the glucuronide and sulfate conjugates of the quinol form of MitoQ10.

IT 444890-41-9
RL: BSU (Biological study, unclassified); BIOL (Biological study) (quantitation and metabolism of mitochondria-targeted antioxidant mitoquinone in rat)
RN 444890-41-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)




REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

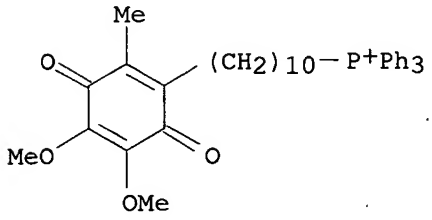
L4 ANSWER 9 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:542355 CAPLUS
DOCUMENT NUMBER: 147:157119
TITLE: Targeting antioxidants to mitochondria: a potential new therapeutic strategy for cardiovascular diseases
AUTHOR(S): Victor, V. M.; Rocha, M.
CORPORATE SOURCE: Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, 28029, Spain
SOURCE: Current Pharmaceutical Design (2007), 13(8), 845-863
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Mitochondria produce large amts. of free radicals and play an important role in the life and death of a cell. Thus, mitochondrial oxidative damage and dysfunction contribute to a number of cell pathologies that manifest themselves through a range of conditions including ischemia-reperfusion injury, sepsis, diabetes, atherosclerosis and; consequently, cardiovascular diseases (CVD). In fact, endothelial dysfunction, characterized by a loss of nitric oxide (NO) bioactivity, occurs early on in the development of atherosclerosis, and dets. future vascular complications. Although the mol. mechanisms responsible for mitochondria-mediated disease processes are not yet clear, oxidative stress seems to play an important role. This review considers the process of CVD from a mitochondrial perspective. Accordingly, strategies for the targeted delivery of antioxidants to mitochondria are being developed. In this review, we will provide a summary of the following areas: the cellular metabolism of reactive oxygen species (ROS) and its role in pathophysiol. processes such as CVD; currently available antioxidants and possible reasons for their efficacy and inefficacy in ameliorating oxidative stress-mediated diseases; recent developments in mitochondrially-targeted antioxidants that concentrate on the matrix-facing surface of the inner mitochondrial membrane and therefore protect against mitochondrial oxidative damage, and their therapeutic potential for future treatment of CVDs. More pre-clin. and clin. studies, however, are necessary in order to evaluate the effectiveness and toxicity of mitochondrially-targeted antioxidants.

IT 444890-41-9, MitoQ
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting antioxidants to mitochondria with a potential new therapeutic strategy for cardiovascular diseases)

RN 444890-41-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-

yl)decyl]triphenyl- (CA INDEX NAME)

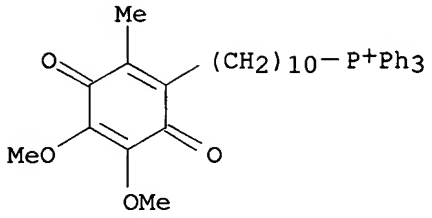


REFERENCE COUNT: 156 THERE ARE 156 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:522753 CAPLUS
DOCUMENT NUMBER: 147:202729
TITLE: Mitochondrial targeting of quinones: Therapeutic implications
AUTHOR(S): Cocheme, Helena M.; Kelso, Geoffrey F.; James, Andrew M.; Ross, Meredith F.; Trnka, Jan; Mahendiran, Thabo; Asin-Cayuela, Jordi; Blaikie, Frances H.; Manas, Abdul-Rahman B.; Porteous, Carolyn M.; Adlam, Victoria J.; Smith, Robin A. J.; Murphy, Michael P.
CORPORATE SOURCE: MRC Dunn Human Nutrition Unit, Cambridge, CB2 2XY, UK
SOURCE: Mitochondrion (2007), 7(Suppl.), S94-S102
CODEN: MITOCN; ISSN: 1567-7249
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Mitochondrial oxidative damage contributes to a range of degenerative diseases. Ubiquinones have been shown to protect mitochondria from oxidative damage, but only a small proportion of externally administered ubiquinone is taken up by mitochondria. Conjugation of the lipophilic triphenylphosphonium cation to a ubiquinone moiety has produced a compound, MitoQ, which accumulates selectively into mitochondria. MitoQ passes easily through all biol. membranes and, because of its pos. charge, is accumulated several hundred-fold within mitochondria driven by the mitochondrial membrane potential. MitoQ protects mitochondria against oxidative damage in vitro and following oral delivery, and may therefore form the basis for mitochondria-protective therapies.

IT 444890-41-9, MitoQ
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mitochondrial targeting of quinones and therapeutic implications)
RN 444890-41-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)




REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:513564 CAPLUS
DOCUMENT NUMBER: 147:160001
TITLE: Interaction of the Mitochondria-targeted Antioxidant MitoQ with Phospholipid Bilayers and Ubiquinone Oxidoreductases
AUTHOR(S): James, Andrew M.; Sharpley, Mark S.; Manas, Abdul-Rahman B.; Frerman, Frank E.; Hirst, Judy; Smith, Robin A. J.; Murphy, Michael P.
CORPORATE SOURCE: Medical Research Council Dunn Human Nutrition Unit, Cambridge, CB2 2XY, UK
SOURCE: Journal of Biological Chemistry (2007), 282(20), 14708-14718
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

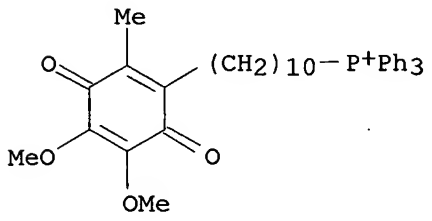
AB MitoQ10 is a ubiquinone that accumulates within mitochondria driven by a conjugated lipophilic triphenylphosphonium cation (TPP+). Once there, MitoQ10 is reduced to its active ubiquinol form, which has been used to prevent mitochondrial oxidative damage and to infer the involvement of reactive oxygen species in signaling pathways. Here we show MitoQ10 is effectively reduced by complex II, but is a poor substrate for complex I, complex III, and electron-transferring flavoprotein (ETF):quinone oxidoreductase (ETF-QOR). This differential reactivity could be explained if the bulky TPP+ moiety sterically hindered access of the ubiquinone group to enzyme active sites with a long, narrow access channel. Using a combination of mol. modeling and an uncharged analog of MitoQ10 with similar sterics (tritylQ10), we infer that the interaction of MitoQ10 with complex I and ETF-QOR, but not complex III, is inhibited by its bulky TPP+ moiety. To explain its lack of reactivity with complex III we show that the TPP+ moiety of MitoQ10 is ineffective at quenching pyrene fluorophors deeply buried within phospholipid bilayers and thus is positioned near the membrane surface. This superficial position of the TPP+ moiety, as well as the low solubility of MitoQ10 in non-polar organic solvents, suggests that the concentration of the entire MitoQ10 mol. in the membrane core is very limited. As overlaying MitoQ10 onto the structure of complex III indicates that MitoQ10 cannot react with complex III without its TPP+ moiety entering the low dielec. of the membrane core, we conclude that the TPP+ moiety does anchor the tethered ubiquinol group out of reach of the active site(s) of complex III, thus explaining its slow oxidation In contrast the ubiquinone moiety of MitoQ10 is able to quench fluorophors deep within the membrane

core, indicating a high concentration of the ubiquinone moiety within the membrane and explaining its good anti-oxidant efficacy. These findings will facilitate the rational design of future mitochondria-targeted mols.

IT 444890-41-9, MitoQ
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(interaction of mitochondria-targeted antioxidant MitoQ with phospholipid bilayers and ubiquinone oxidoreductases)

RN 444890-41-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)




REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:407185 CAPLUS
DOCUMENT NUMBER: 147:63256
TITLE: Transport and metabolism of MitoQ10, a mitochondria-targeted antioxidant, in Caco-2 cell monolayers
AUTHOR(S): Li, Yan; Fawcett, J. Paul; Zhang, Hu; Tucker, Ian G.
CORPORATE SOURCE: School of Pharmacy, University of Otago, Dunedin, N. Z.
SOURCE: Journal of Pharmacy and Pharmacology (2007), 59(4), 503-511
CODEN: JPPMAB; ISSN: 0022-3573
PUBLISHER: Pharmaceutical Press
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 147:63256

AB Mitoquinone (MitoQ10 mesylate) is a mitochondria-targeted antioxidant formulated for oral administration in the treatment of neurodegenerative diseases. We have investigated the absorption and metabolism of MitoQ10 in Caco-2 cell monolayers. The intracellular accumulation of MitoQ10 was 18-41% of the total amount of MitoQ10 added. Some of the intracellular MitoQ10 was reduced to mitoquinol and subsequently metabolized to glucuronide and sulfate conjugates. Transport of MitoQ10 was polarized with the apparent permeability (Papp) from basolateral (BL) to apical (AP) (PappBL→AP) being >2.5-fold the Papp from apical to basolateral (PappAP→BL). In the presence of 4% bovine serum albumin on the basolateral side, the PappAP→BL value increased 7-fold compared with control. The PappBL→AP value decreased by 26%, 31%, and 61% in the presence of verapamil 100 μM, ciclosporin 10 and 30 μM, resp., whereas the PappAP→BL value increased 71% in the presence of ciclosporin 30 μM. Apical efflux of mitoquinol sulfate and mitoquinol glucuronide conjugates was significantly decreased by ciclosporin 30 μM and the breast cancer receptor protein

(BCRP) inhibitor, reserpine 25 μM, resp. These results suggested that the bioavailability of MitoQ10 may be limited by intracellular metabolism and the action of P-glycoprotein and BCRP. However, the dramatic increase in absorptive Papp in the presence of bovine serum albumin on the receiver side suggests these barrier functions may be less significant in-vivo.

IT 845959-50-4, Mitoquinone mesylate
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(transport and metabolism of MitoQ10 as mitochondria-targeted antioxidant, in Caco-2 cell monolayers)

RN 845959-50-4 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

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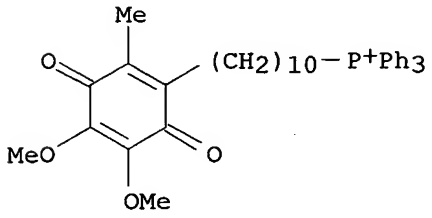


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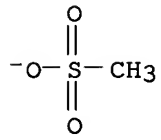



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

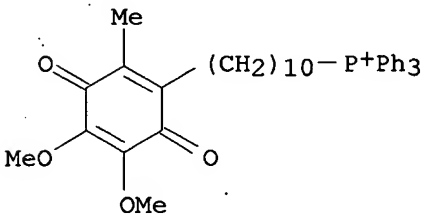
L4 ANSWER 13 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:70572 CAPLUS
DOCUMENT NUMBER: 146:182912
TITLE: High Concentration of Antioxidants N-Acetylcysteine and Mitoquinone-Q Induces Intercellular Adhesion Molecule 1 and Oxidative Stress by Increasing Intracellular Glutathione
AUTHOR(S): Mukherjee, Tapan K.; Mishra, Anurag K.; Mukhopadhyay, Srirupa; Hoidal, John R.
CORPORATE SOURCE: Department of Internal Medicine, Pulmonary Division, University of Utah Health Science Center, Salt Lake

City, UT, 84112, USA
SOURCE: Journal of Immunology (2007), 178(3), 1835-1844
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In endothelial cells, the intracellular level of glutathione is depleted during offering protection against proinflammatory cytokine TNF-α-induced oxidative stress. Administration of anti-inflammatory drugs, i.e., N-acetylcysteine (NAC) or mitoquinone-Q (mito-Q) in low concns. in the human pulmonary aortic endothelial cells offered protection against depletion of reduced glutathione and oxidative stress mediated by TNF-α. However, this study addressed that administration of NAC or mito-Q in high concns. resulted in a biphasic response by initiating an enhanced generation of both reduced glutathione and oxidized glutathione and enhanced production of reactive oxygen species, along with carbonylation and glutathionylation of the cellular proteins. This study further addressed that IκB kinase (IKK), a phosphorylation-dependent regulator of NF-κB, plays an important regulatory role in the TNF-α-mediated induction of the inflammatory cell surface mol. ICAM-1. Of the two catalytic subunits of IKK (IKKα and IKKβ), low concns. of NAC and mito-Q activated IKKα activity, thereby inhibiting the downstream NF-κB and ICAM-1 induction by TNF-α. High concns. of NAC and mito-Q instead caused glutathionylation of IKKα, thereby inhibiting its activity that in turn enhanced the downstream NF-κB activation and ICAM-1 expression by TNF-α. Thus, establishing IKKα as an anti-inflammatory mol. in endothelial cells is another focus of this study. This is the first report that describes a stressful situation in the endothelial cells created by excess of antioxidative and anti-inflammatory agents NAC and mito-Q, resulting in the generation of reactive oxygen species, carbonylation and glutathionylation of cellular proteins, inhibition of IKKα activity, and up-regulation of ICAM-1 expression.

IT 444890-41-9, MitoQ
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(high concentration of antioxidants N-acetylcysteine and mitoquinone-Q induces
ICAM-1 and oxidative stress by increasing intracellular glutathione)

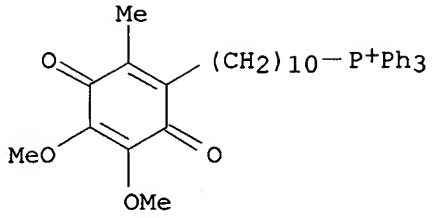
RN 444890-41-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)




REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:1348478 CAPLUS

DOCUMENT NUMBER: 146:178916
TITLE: Reactive Oxygen and Targeted Antioxidant Administration in Endothelial Cell Mitochondria
AUTHOR(S): O'Malley, Yunxia; Fink, Brian D.; Ross, Nicolette C.; Prisinzano, Thomas E.; Sivitz, William I.
CORPORATE SOURCE: Iowa City Veterans Affairs Medical Center, Department of Internal Medicine, Division of Endocrinology and Metabolism and the College of Pharmacy, Division of Medicinal and Natural Products Chemistry, University of Iowa, Iowa City, IA, 52242, USA
SOURCE: Journal of Biological Chemistry (2006), 281(52), 39766-39775
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We used fluorescent probes and EPR to study the mechanism(s) underlying reactive oxygen species (ROS) production by endothelial cell mitochondria and the action of mitoquinol (MitoQ), a mitochondria-targeted antioxidant. ROS measured by fluorescence resulted from complex I superoxide released to the matrix and converted to H2O2. In contrast, EPR largely detected superoxide generated at complex III and effluxed outward. ROS fluorescence by mitochondria fueled by the complex II substrate, succinate, was substantial but markedly inhibited by rotenone. Superoxide, detected by EPR, in succinate-fueled mitochondria was not inhibited by rotenone and likely derived from semiquinone formation at complex III. Mitoquinol decreased H2O2 fluorescence by succinate-fueled mitochondria but had little effect on the EPR signal for superoxide. This was not associated with a detectable decrease in membrane potential. Mitoquinol markedly enhanced ROS fluorescence in mitochondria fueled by the complex I substrates, glutamate and malate. Inhibitor studies suggested that this occurred in complex I, at one or more Q binding pockets. The above effects of mitoquinol were determined in mitochondria isolated and subsequently exposed to the targeted antioxidant. However, similar effects were observed in mitochondria after antecedent exposure to mitoquinol/mitoquinone in culture, suggesting that the agent is retained after isolation of the organelles. In conclusion, ROS production in bovine aortic endothelial cell mitochondria results largely from reverse transport to complex I and through the Q cycle in complex III. Mitoquinol blocks ROS from reverse electron transport but increases superoxide production derived from forward transport. These effects likely occur at one or more Q binding sites in complex I.
IT 444890-41-9, MitoQ
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(MitoQ acts in complex I to block ROS generated by reverse electron transport but increases superoxide production associated with forward electron transport)
RN 444890-41-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)




REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:1067714 CAPLUS
DOCUMENT NUMBER: 145:419306
TITLE: Preparation of mitoquinone derivatives as mitochondrially targeted antioxidants
INVENTOR(S): Taylor, Kenneth Martin; Smith, Robin A. J.
PATENT ASSIGNEE(S): Antipodean Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 57pp., Cont.-in-part of U.S. Ser. No. 172,916.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| US 20060229278 | A1 | 20061012 | US 2006-355518 | 20060215 |
| WO 9926954 | A1 | 19990603 | WO 1998-NZ173 | 19981125 |
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| US 6331532 | B1 | 20011218 | US 2000-577877 | 20000525 |
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SN, TD, TG

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PRIORITY APPLN. INFO.:

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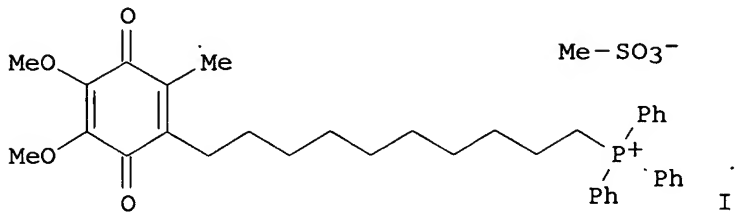
| WO 1998-NZ173 | A2 19981125 |
| US 2000-577877 | A1 20000525 |
| US 2001-968838 | B1 20011003 |
| US 2002-272914 | B1 20021018 |
| NZ 2003-527800 | A 20030822 |
| NZ 2003-529153 | A 20031023 |
| US 2003-722542 | B1 20031128 |
| NZ 2004-533556 | A 20040614 |
| WO 2004-NZ196 | A1 20040823 |
| US 2005-172916 | A2 20050705 |
| NZ 1997-329255 | A 19971125 |
| AU 1999-16965 | A3 19981125 |
| NZ 1998-329255 | A 19981125 |

OTHER SOURCE(S): MARPAT 145:419306

GI




I

AB This invention relates to pharmaceutically acceptable amphiphilic antioxidant compds., compns. and dosage forms comprising the compds. The compds., compns., dosage forms, uses and methods are useful in the treatment of diseases or conditions associated with oxidative stress. Thus, I 1:2 complex β-cyclodextrin with was prepared, and tested for stability and pharmacokinetics.

IT 845959-56-0P
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of mitoquinone triphenylphosphonium derivs. as mitochondrially targeted antioxidants)

RN 845959-56-0 CAPLUS

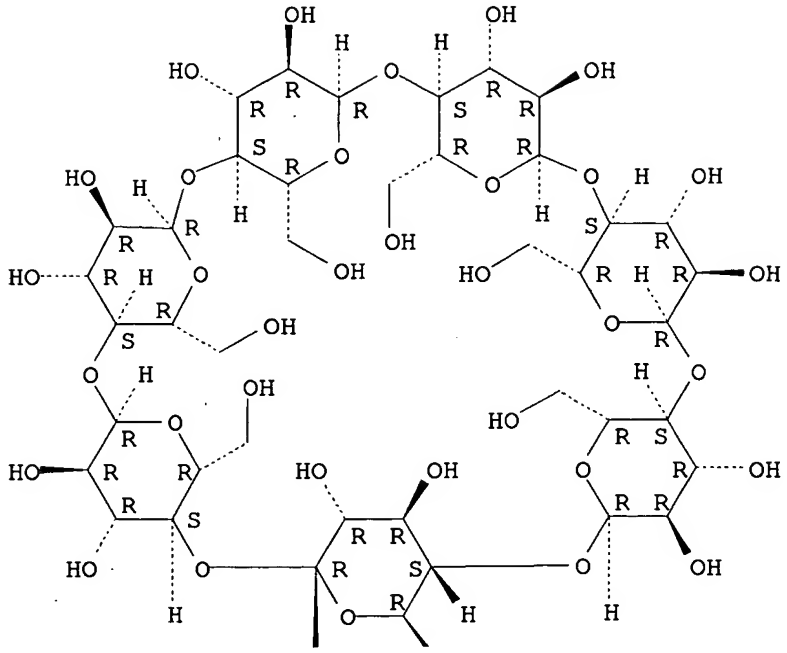
CN β-Cyclodextrin, compd. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium methanesulfonate (2:1) (9CI) (CA INDEX NAME)

CM 1

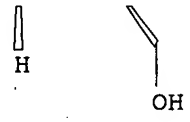
CRN 7585-39-9
CMF C42 H70 O35

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A

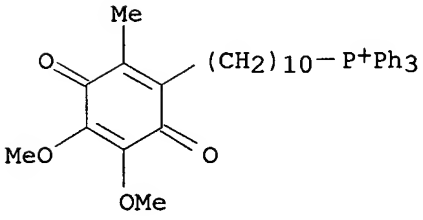


CM 2

CRN 845959-50-4
CMF C37 H44 O4 P . C H3 O3 S

CM 3

CRN 444890-41-9
CMF C37 H44 O4 P



CM 4

CRN 16053-58-0
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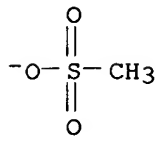


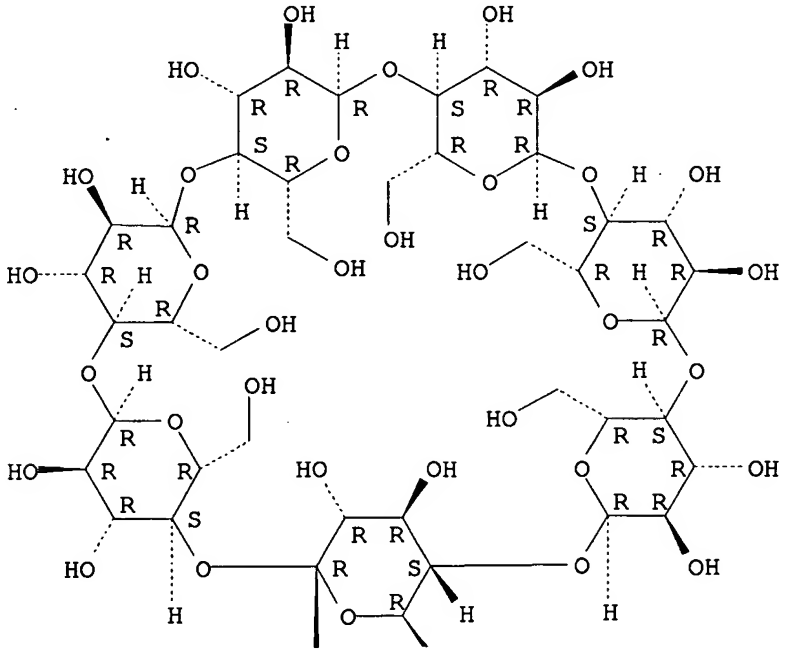
IT 845959-52-6P 911841-84-4P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of mitoquinone triphenylphosphonium derivs. as mitochondrially targeted antioxidants)
RN 845959-52-6 CAPLUS
CN β-Cyclodextrin, compd. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium methanesulfonate (1:1) (9CI) (CA INDEX NAME)

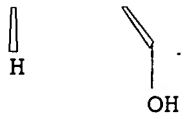
CM 1

CRN 7585-39-9
CMF C42 H70 O35

Absolute stereochemistry.

PAGE 1-A





CM 2

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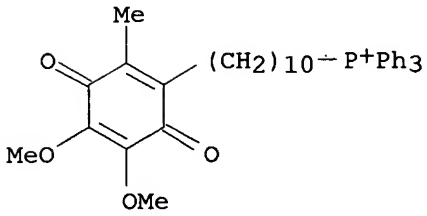
CMF C37 H44 O4 P . C H3 O3 S

CM 3

CRN 444890-41-9
CMF C37 H44 O4 P



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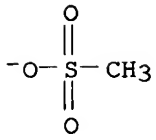


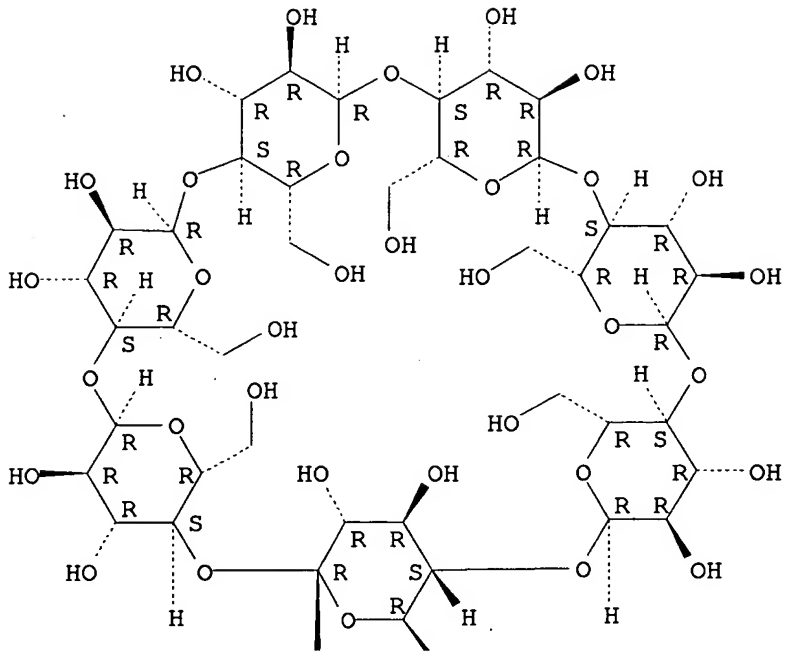
RN 911841-84-4 CAPLUS
CN β-Cyclodextrin, compd. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium methanesulfonate (4:1) (9CI) (CA INDEX NAME)

CM 1

CRN 7585-39-9
CMF C42 H70 O35

Absolute stereochemistry.

PAGE 1-A



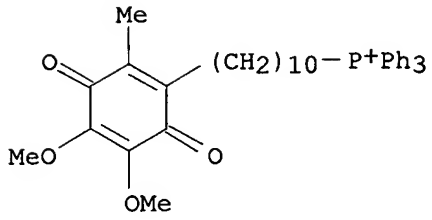
PAGE 2-A

CM 2

CRN 845959-50-4
CMF C37 H44 O4 P . C H3 O3 S

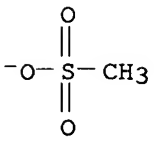
CM 3

CRN 444890-41-9
CMF C37 H44 O4 P



CM 4

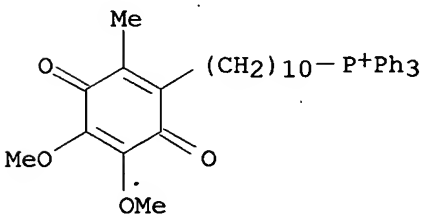
CRN 16053-58-0
CMF C H3 O3 S



IT 845959-50-4P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of mitoquinone triphenylphosphonium derivs. as mitochondrially targeted antioxidants)
RN 845959-50-4 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

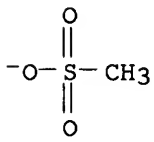
CM 1

CRN 444890-41-9
CMF C37 H44 O4 P



CM 2

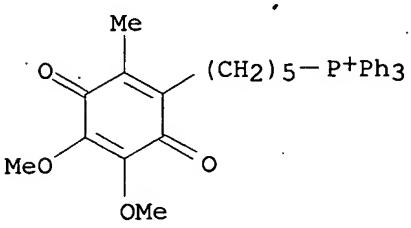
CRN 16053-58-0
CMF C H3 O3 S



IT 764723-90-2P 764723-92-4P 845959-58-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

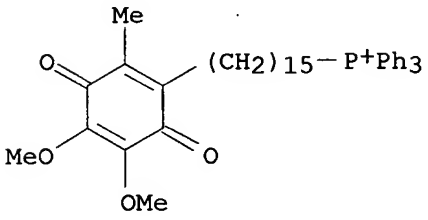
(Uses)
(preparation of mitoquinone triphenylphosphonium derivs. as mitochondrially targeted antioxidants)

RN 764723-90-2 CAPLUS
CN Phosphonium, [5-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentyl]triphenyl-, iodide (1:1) (CA INDEX NAME)




● $I^-$

RN 764723-92-4 CAPLUS
CN Phosphonium, [15-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentadecyl]triphenyl-, bromide (1:1) (CA INDEX NAME)




● $Br^-$

RN 845959-58-2 CAPLUS
CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

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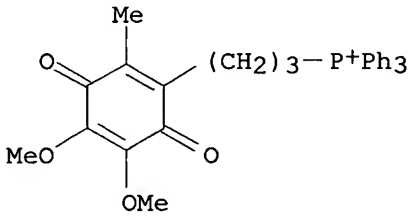
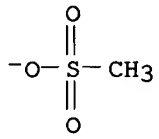
CRN 794485-93-1
CMF C30 H30 O4 P

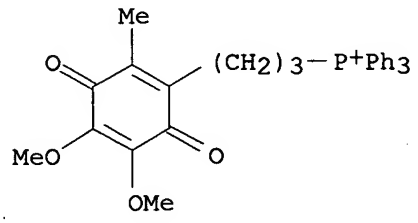


CM 2

CRN 16053-58-0
CMF C H3 O3 S

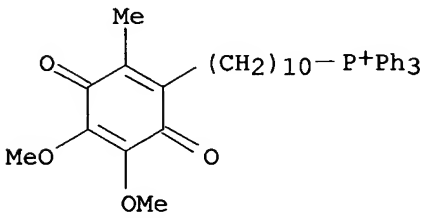


IT 845959-57-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of mitoquinone triphenylphosphonium derivs. as mitochondrially targeted antioxidants)
RN 845959-57-1 CAPLUS
CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



L4 ANSWER 16 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:202663 CAPLUS
DOCUMENT NUMBER: 145:202743
TITLE: The effects of exogenous antioxidants on lifespan and oxidative stress resistance in Drosophila melanogaster
AUTHOR(S): Magwere, Tapiwanashe; West, Melanie; Riyahi, Kumars; Murphy, Michael P.; Smith, Robin A. J.; Partridge, Linda

CORPORATE SOURCE: Centre for Research on Aging, Department of Biology, University College London, London, WC1E 6BT, UK
SOURCE: Mechanisms of Ageing and Development (2006), 127(4), 356-370
CODEN: MAGDA3; ISSN: 0047-6374
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We used the fruit fly Drosophila melanogaster to test the effects of feeding the superoxide dismutase (SOD) mimetic drugs Euk-8 and -134 and the mitochondria-targeted mitoquinone (MitoQ) on lifespan and oxidative stress resistance of wild type and SOD-deficient flies. Our results reaffirm the findings by other workers that exogenous antioxidant can rescue pathol. associated with compromised defences to oxidative stress, but fail to extend the lifespan of normal, wild type animals. All three drugs showed a dose-dependent increase in toxicity in wild type flies, an effect that was exacerbated in the presence of the redox-cycling drug paraquat. However, important findings from this study were that in SOD-deficient flies, where the antioxidant drugs increased lifespan, the effects were sex-specific and, for either sex, the effects were also variable depending on (1) the stage of development from which the drugs were given, and (2) the magnitude of the dose. These findings place significant constraints on the role of oxidative stress in normal aging.
IT 444890-41-9, MitoQ
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antioxidant drug, mitochondria-targeted mitoquinone dose-dependently increased toxicity in wild type flies while it increased lifespan in superoxide dismutase-deficient Drosophila melanogaster)
RN 444890-41-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)




REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:51133 CAPLUS
DOCUMENT NUMBER: 144:121851
TITLE: Use of mitochondrially targeted antioxidant -lipophilic cation conjugate in the treatment of liver diseases and epithelial cancers.
INVENTOR(S): Froehlich, Eleonore; Kvietikova, Ivica; Zatloukal, Kurt; Schatz, Gottfried; Denk, Helmut; Stumptner, Cornelia; Buck, Charles

PATENT ASSIGNEE(S): Oridis Biomed Forschungs- und Entwicklungs G.m.b.H., Austria
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 2006005759 | A2 | 20060119 | WO 2005-EP53338 | | 20050712 |
| WO 2006005759 | A3 | 20060511 | | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | | |
| AU 2005261654 | A1 | 20060119 | AU 2005-261654 | | 20050712 |
| CA 2573456 | A1 | 20060119 | CA 2005-2573456 | | 20050712 |
| EP 1765413 | A2 | 20070328 | EP 2005-775873 | | 20050712 |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR | | | | | |
| CN 1997403 | A | 20070711 | CN 2005-80023193 | | 20050712 |
| JP 2008506667 | T | 20080306 | JP 2007-520833 | | 20050712 |
| KR 2007030815 | A | 20070316 | KR 2006-725659 | | 20061206 |
| US 20070225255 | A1 | 20070927 | US 2007-632149 | | 20070212 |
| PRIORITY APPLN. INFO.: | | | EP 2004-103318 | A | 20040713 |
| | | | WO 2005-EP53338 | W | 20050712 |

OTHER SOURCE(S): MARPAT 144:121851

AB The invention discloses the use of a mitochondrially targeted antioxidant, e.g. derivs. of vitamin E, coenzyme Q10 or a glutathione peroxidase mimetic, in the treatment and prevention of liver diseases and/or epithelial cancers. The invention also discloses pharmaceutical compns. containing the antioxidant(s) intended for such use. Furthermore the invention relates to the manufacture of medicaments containing the antioxidant(s) useful for such prevention and treatment. Compds. of the invention comprise a lipophilic cation covalently coupled to an antioxidant moiety, e.g. (Ph)3P+XR·Z- (X = linking group; R = antioxidant moiety; Z- = anion).

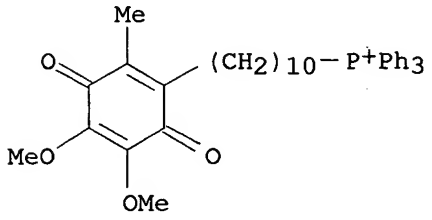
IT 873653-01-1 873653-02-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mitochondrially targeted antioxidant-lipophilic cation conjugate for treatment of liver disease and epithelial cancer)

RN 873653-01-1 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide, mixt. with [10-(3,6-dihydroxy-4,5-dimethoxy-2-methylphenyl)decyl]triphenylphosphonium bromide (9CI) (CA INDEX NAME)

CM 1

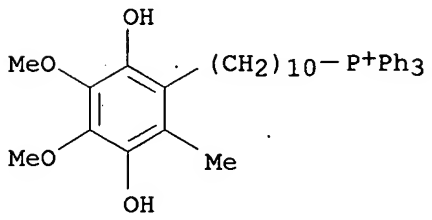
CRN 336184-91-9
CMF C37 H44 O4 P . Br



● $Br^-$

CM 2

CRN 299975-19-2
CMF C37 H46 O4 P . Br



● $Br^-$

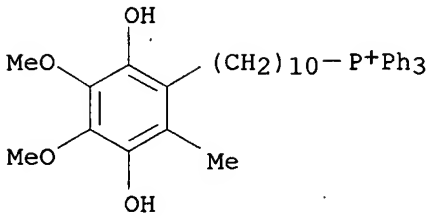
RN 873653-02-2 CAPLUS
CN Phosphonium, [10-(3,6-dihydroxy-4,5-dimethoxy-2-methylphenyl)decyl]triphenyl-, methanesulfonate, mixt. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium methanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 845959-55-9
CMF C37 H46 O4 P . C H3 O3 S

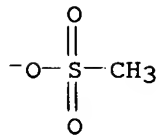
CM 2

CRN 747398-82-9
CMF C37 H46 O4 P



CM 3

CRN 16053-58-0
CMF C H3 O3 S

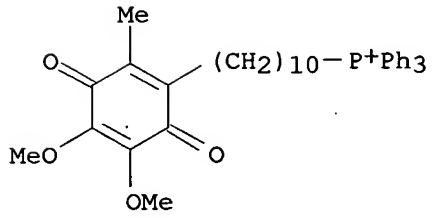


CM 4

CRN 845959-50-4
CMF C37 H44 O4 P . C H3 O3 S

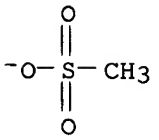
CM 5

CRN 444890-41-9
CMF C37 H44 O4 P



CM 6

CRN 16053-58-0
CMF C H3 O3 S

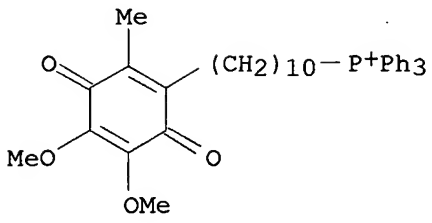


L4 ANSWER 18 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:584282 CAPLUS
DOCUMENT NUMBER: 143:241657
TITLE: Targeting an antioxidant to mitochondria decreases cardiac ischemia-reperfusion injury
AUTHOR(S): Adlam, Victoria J.; Harrison, Joanne C.; Porteous, Carolyn M.; James, Andrew M.; Smith, Robin A. J.; Murphy, Michael P.; Sammut, Ivan A.
CORPORATE SOURCE: Department of Chemistry, University of Otago, Dunedin, N. Z.
SOURCE: FASEB Journal (2005), 19(9), 1088-1095
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mitochondrial oxidative damage contributes to a wide range of pathologies, including cardiovascular disorders and neurodegenerative diseases. Therefore, protecting mitochondria from oxidative damage should be an effective therapeutic strategy. However, conventional antioxidants have limited efficacy due to the difficulty of delivering them to mitochondria in situ. To overcome this problem, we developed mitochondria-targeted antioxidants, typified by MitoQ, which comprises a lipophilic triphenylphosphonium (TPP) cation covalently attached to a ubiquinol antioxidant. Driven by the large mitochondrial membrane potential, the TPP cation concs. MitoQ several hundred-fold within mitochondria, selectively preventing mitochondrial oxidative damage. To test whether MitoQ was active in vivo, we chose a clin. relevant form of mitochondrial oxidative damage: cardiac ischemia-reperfusion injury. Feeding MitoQ to rats significantly decreased heart dysfunction, cell death, and mitochondrial damage after ischemia-reperfusion. This protection was due to the antioxidant activity of MitoQ within mitochondria, as an untargeted antioxidant was ineffective and accumulation of the TPP cation alone gave no protection. Therefore, targeting antioxidants to mitochondria in vivo is a promising new therapeutic strategy in the wide range of human diseases such as Parkinson's disease, diabetes, and Friedreich's ataxia where mitochondrial oxidative damage underlies the pathol.

IT 444890-41-9, MitoQ
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting an antioxidant to mitochondria decreases cardiac ischemia-reperfusion injury)

RN 444890-41-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)




REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

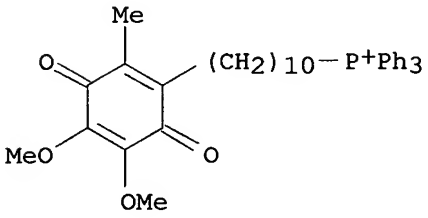
L4 ANSWER 19 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:463624 CAPLUS
DOCUMENT NUMBER: 143:148390
TITLE: Interactions of Mitochondria-targeted and Untargeted Ubiquinones with the Mitochondrial Respiratory Chain and Reactive Oxygen Species: implications for the use of exogenous ubiquinones as therapies and experimental tools
AUTHOR(S): James, Andrew M.; Cocheme, Helena M.; Smith, Robin A. J.; Murphy, Michael P.
CORPORATE SOURCE: Medical Research Council Dunn Human Nutrition Unit, Cambridge, CB2 2XY, UK
SOURCE: Journal of Biological Chemistry (2005), 280(22), 21295-21312
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Antioxidants, such as ubiquinones, are widely used in mitochondrial studies as both potential therapies and useful research tools. However, the effects of exogenous ubiquinones can be difficult to interpret because they can also be pro-oxidants or electron carriers that facilitate respiration. Recently we developed a mitochondria-targeted ubiquinone (MitoQ10) that accumulates within mitochondria. MitoQ10 has been used to prevent mitochondrial oxidative damage and to infer the involvement of mitochondrial reactive oxygen species in signaling pathways. However, uncertainties remain about the mitochondrial reduction of MitoQ10, its oxidation by the respiratory chain, and its pro-oxidant potential. Therefore, we compared MitoQ analogs of varying alkyl chain lengths (MitoQn, n = 3-15) with untargeted exogenous ubiquinones. We found that MitoQ10 could not restore respiration in ubiquinone-deficient mitochondria because oxidation of MitoQ analogs by complex III was minimal. Complex II and glycerol 3-phosphate dehydrogenase reduced MitoQ analogs, and the rate depended on chain length. Because of its rapid reduction and negligible oxidation, MitoQ10 is a more effective antioxidant against lipid peroxidn., peroxynitrite and superoxide. Paradoxically, exogenous ubiquinols also autoxidize to generate superoxide, but this requires their deprotonation in the aqueous phase. Consequently, in the presence of phospholipid bilayers, the rate of autoxidn. is proportional to ubiquinol hydrophilicity. Superoxide production by MitoQ10 was insufficient to damage aconitase but did lead to hydrogen peroxide production and nitric oxide consumption, both of which may affect cell signaling pathways. Our results comprehensively

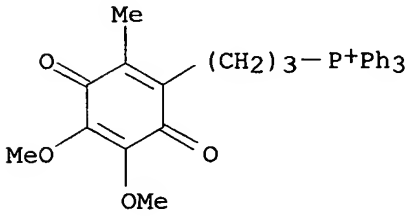
describe the interaction of exogenous ubiquinones with mitochondria and have implications for their rational design and use as therapies and as research tools to probe mitochondrial function.

IT 444890-41-9 794485-93-1 794485-94-2
794485-95-3
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(interactions of mitochondria-targeted and untargeted ubiquinones with the mitochondrial respiratory chain and reactive oxygen species)

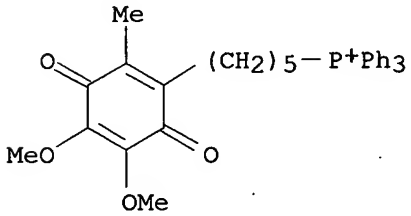
RN 444890-41-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



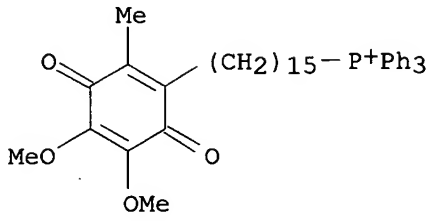

RN 794485-93-1 CAPLUS
CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl- (CA INDEX NAME)




RN 794485-94-2 CAPLUS
CN Phosphonium, [5-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentyl]triphenyl- (CA INDEX NAME)




RN 794485-95-3 CAPLUS
CN Phosphonium, [15-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentadecyl]triphenyl- (CA INDEX NAME)




REFERENCE COUNT: 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:182678 CAPLUS
DOCUMENT NUMBER: 142:254662
TITLE: Mitoquinone derivatives used as mitochondrially targeted antioxidants, and preparation thereof
INVENTOR(S): Murphy, Michael Patrick; Smith, Robin
PATENT ASSIGNEE(S): Antipodean Biotechnology Limited, N. Z.
SOURCE: PCT Int. Appl., 102 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005019233 | A1 | 20050303 | WO 2004-NZ197 | 20040823 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2003204144 | A1 | 20030612 | AU 2003-204144 | 20030512 |
| AU 2003204144 | B2 | 20070301 | | |
| US 20070238709 | A1 | 20071011 | US 2007-568654 | 20070222 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| NZ 2003-527800 | A | 20030822 |
| NZ 2003-529153 | A | 20031023 |
| NZ 2004-533555 | A | 20040614 |
| AU 1999-16965 | A3 | 19981125 |
| NZ 1998-329255 | A | 19981125 |
| WO 2004-NZ197 | W | 20040823 |

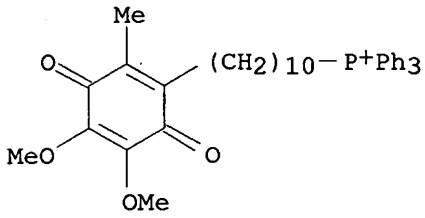
OTHER SOURCE(S): CASREACT 142:254662; MARPAT 142:254662

AB This invention discloses methods to screen for, identify, select, and synthesize amphiphilic mitochondrially targeted antioxidant compds., and compns., dosage forms, and methods reliant on these compds. The compds. are all mitoquinone derivs., being methoxyphenyl alkyl triphenylphosphonium or methoxy dioxocyclohexadiene alkyl triphenylphosphonium derivs. The compds., compns., dosage forms and

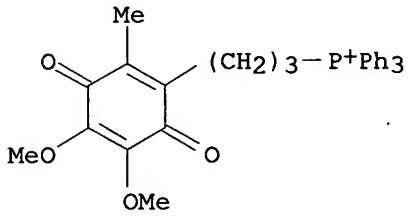
methods are useful in e.g. the treatment of diseases or conditions associated with oxidative stress.

IT 444890-41-9 794485-93-1 794485-94-2
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mitoquinone derivative preparation for mitochondrially targeted antioxidant)

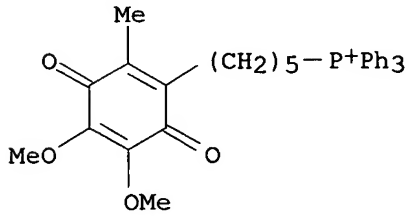
RN 444890-41-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)




RN 794485-93-1 CAPLUS
CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl- (CA INDEX NAME)

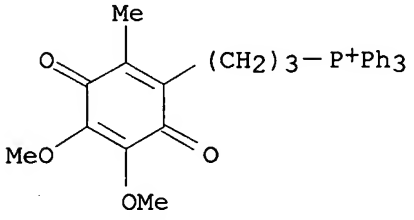



RN 794485-94-2 CAPLUS
CN Phosphonium, [5-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentyl]triphenyl- (CA INDEX NAME)

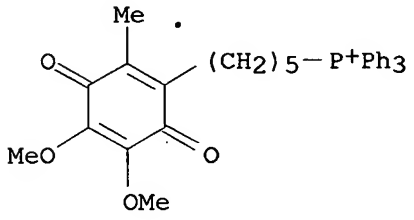



IT 845959-57-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(mitoquinone derivative preparation for mitochondrially targeted antioxidant)

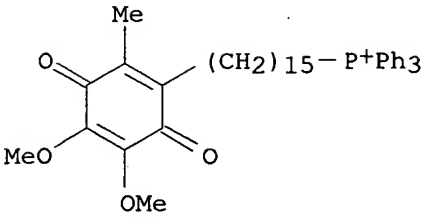
RN 845959-57-1 CAPLUS
CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



IT 764723-90-2P 764723-92-4P 845959-58-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(mitoquinone derivative preparation for mitochondrially targeted antioxidant)
RN 764723-90-2 CAPLUS
CN Phosphonium, [5-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentyl]triphenyl-, iodide (1:1) (CA INDEX NAME)



RN 764723-92-4 CAPLUS
CN Phosphonium, [15-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentadecyl]triphenyl-, bromide (1:1) (CA INDEX NAME)

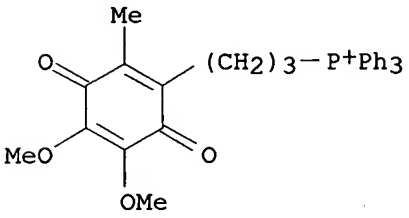


● $Br^-$

RN 845959-58-2 CAPLUS
CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

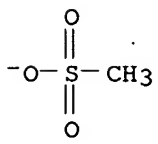
CM 1

CRN 794485-93-1
CMF C30 H30 O4 P

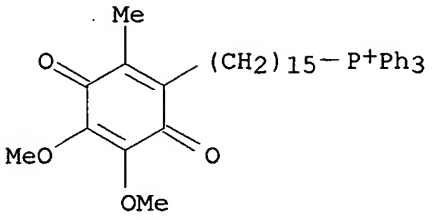


CM 2

CRN 16053-58-0
CMF C H3 O3 S



IT 794485-95-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mitoquinone derivative preparation for mitochondrially targeted antioxidant)
RN 794485-95-3 CAPLUS
CN Phosphonium, [15-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentadecyl]triphenyl- (CA INDEX NAME)




REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 21 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:182677 CAPLUS
DOCUMENT NUMBER: 142:254661
TITLE: Mitoquinone derivatives used as mitochondrially targeted antioxidants, and preparation thereof
INVENTOR(S): Taylor, Kenneth Martin; Smith, Robin
PATENT ASSIGNEE(S): Antipodean Biotechnology Limited, N. Z.
SOURCE: PCT Int. Appl., 143 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005019232 | A1 | 20050303 | WO 2004-NZ196 | 20040823 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2003204144 | A1 | 20030612 | AU 2003-204144 | 20030512 |
| AU 2003204144 | B2 | 20070301 | | |
| AU 2004266988 | A1 | 20050303 | AU 2004-266988 | 20040823 |
| CA 2536546 | A1 | 20050303 | CA 2004-2536546 | 20040823 |
| EP 1664069 | A1 | 20060607 | EP 2004-775122 | 20040823 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK | | | | |
| CN 1839142 | A | 20060927 | CN 2004-80024155 | 20040823 |
| BR 2004013742 | A | 20061024 | BR 2004-13742 | 20040823 |
| JP 2007503387 | T | 20070222 | JP 2006-523805 | 20040823 |
| US 20060229278 | A1 | 20061012 | US 2006-355518 | 20060215 |
| MX 2006PA02114 | A | 20061207 | MX 2006-PA2114 | 20060222 |
| NO 2006000977 | A | 20060519 | NO 2006-977 | 20060228 |
| US 20080161267 | A1 | 20080703 | US 2006-568655 | 20060831 |
| PRIORITY APPLN. INFO.: | | | NZ 2003-527800 A | 20030822 |
| | | | NZ 2003-529153 A | 20031023 |

| | | |
|---|---|---|
| NZ 2004-533556 | A | 20040614 |
| AU 1999-16965 | A3 | 19981125 |
| NZ 1998-329255 | A | 19981125 |
| WO 1998-NZ173 | A2 | 19981125 |
| US 2000-577877 | A1 | 20000525 |
| US 2001-968838 | B1 | 20011003 |
| US 2002-272914 | B1 | 20021018 |
| US 2003-722542 | B1 | 20031128 |
| WO 2004-NZ196 | W | 20040823 |
| US 2005-172916 | A2 | 20050705 |

OTHER SOURCE(S): CASREACT 142:254661; MARPAT 142:254661

AB The invention discloses pharmaceutically acceptable amphiphilic antioxidant compds., compns., and dosage forms comprising these compds., and methods and uses reliant on these compds. The compds. are all mitoquinone derivs., being methoxyphenyl alkyl triphenylphosphonium or methoxy dioxocyclohexadiene alkyl triphenylphosphonium derivs. The compds., compns., dosage forms, uses, and methods are useful in e..g. the treatment of diseases or conditions associated with oxidative stress.

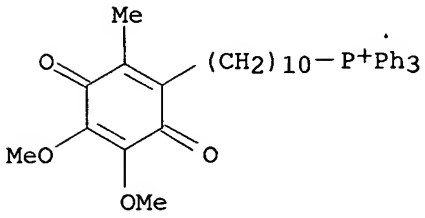
IT 845959-50-4P
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(mitoquinone derivative preparation for mitochondrially targeted antioxidant)

RN 845959-50-4 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

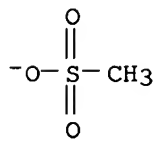
CM 1

CRN 444890-41-9
CMF C37 H44 O4 P




CM 2

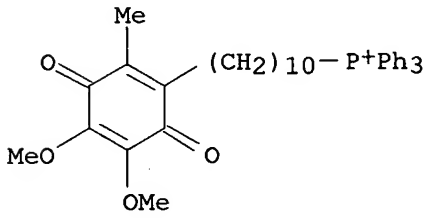
CRN 16053-58-0
CMF C H3 O3 S



IT 845959-59-3P
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(mitoquinone derivative preparation for mitochondrially targeted antioxidant)
RN 845959-59-3 CAPLUS
CN β-Cyclodextrin, compd. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium (2:1) (9CI) (CA INDEX NAME)

CM 1

CRN 444890-41-9
CMF C37 H44 O4 P

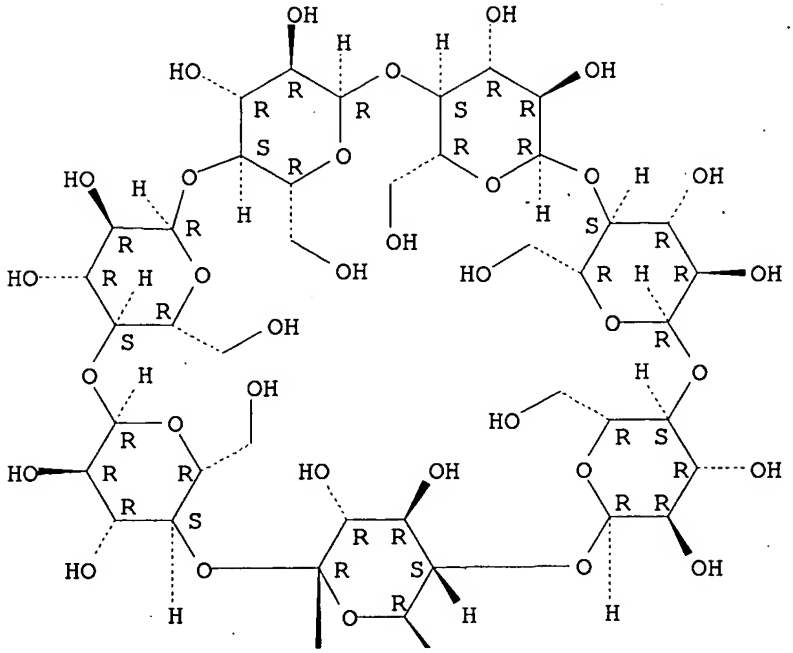



CM 2

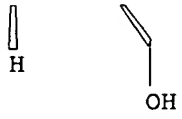
CRN 7585-39-9
CMF C42 H70 O35

Absolute stereochemistry.

PAGE 1-A



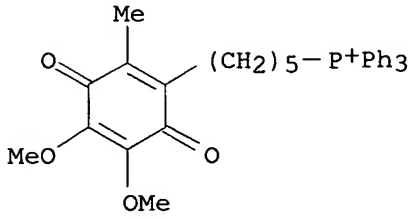
PAGE 2-A



IT 764723-90-2P 764723-92-4P 845959-58-2P
845959-60-6P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(mitoquinone derivative preparation for mitochondrially targeted antioxidant)

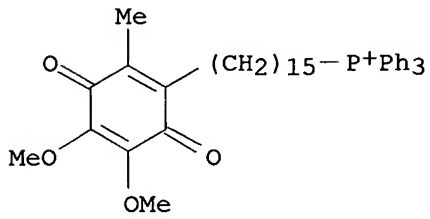
RN 764723-90-2 CAPLUS

CN Phosphonium, [5-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentyl]triphenyl-, iodide (1:1) (CA INDEX NAME)



● $I^-$

RN 764723-92-4 CAPLUS
CN Phosphonium, [15-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentadecyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



● $Br^-$

RN 845959-58-2 CAPLUS
CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

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CRN 794485-93-1
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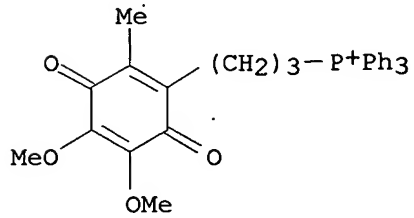
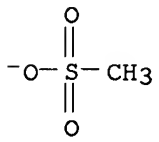


CM 2

CRN 16053-58-0

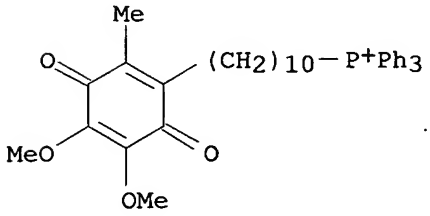
CMF C H3 O3 S



RN 845959-60-6 CAPLUS
CN β-Cyclodextrin, compd. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium (4:1) (9CI) (CA INDEX NAME)

CM 1

CRN 444890-41-9
CMF C37 H44 O4 P

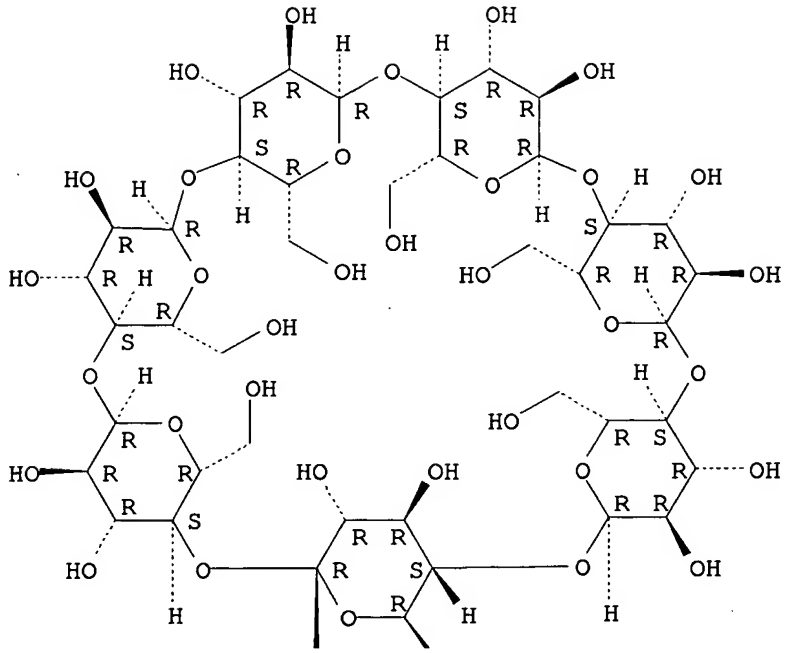


CM 2

CRN 7585-39-9
CMF C42 H70 O35

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A

IT 845959-56-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(mitoquinone derivative preparation for mitochondrially targeted antioxidant)

RN 845959-56-0 CAPLUS

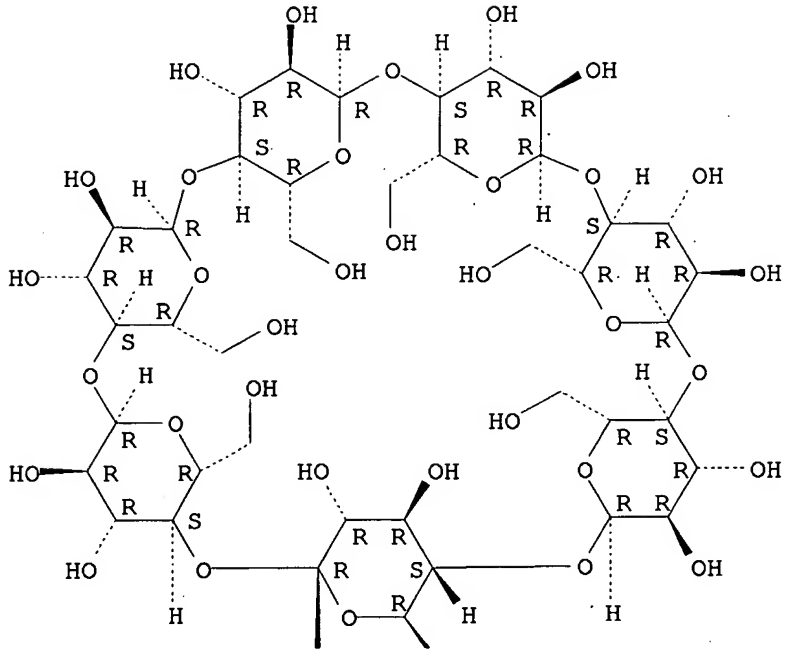
CN β-Cyclodextrin, compd. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium methanesulfonate (2:1) (9CI) (CA INDEX NAME)

CM 1

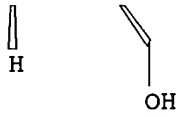
CRN 7585-39-9
CMF C42 H70 O35

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A

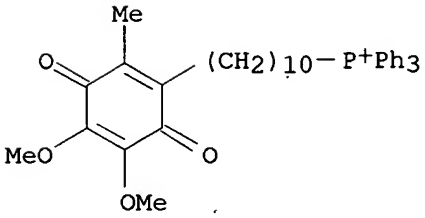


CM 2

CRN 845959-50-4
CMF C37 H44 O4 P . C H3 O3 S

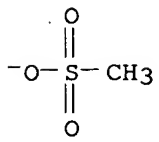
CM 3

CRN 444890-41-9
CMF C37 H44 O4 P

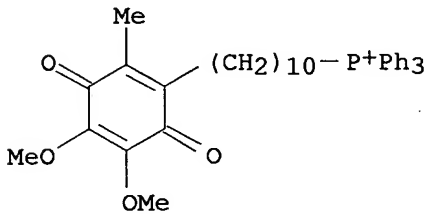


CM 4

CRN 16053-58-0
CMF C H3 O3 S



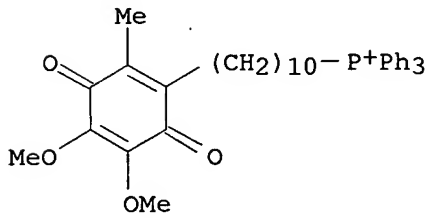
IT 444890-41-9 845959-51-5 845959-52-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mitoquinone derivative preparation for mitochondrially targeted antioxidant)
RN 444890-41-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)



RN 845959-51-5 CAPLUS
CN β-Cyclodextrin, compd. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 444890-41-9
CMF C37 H44 O4 P

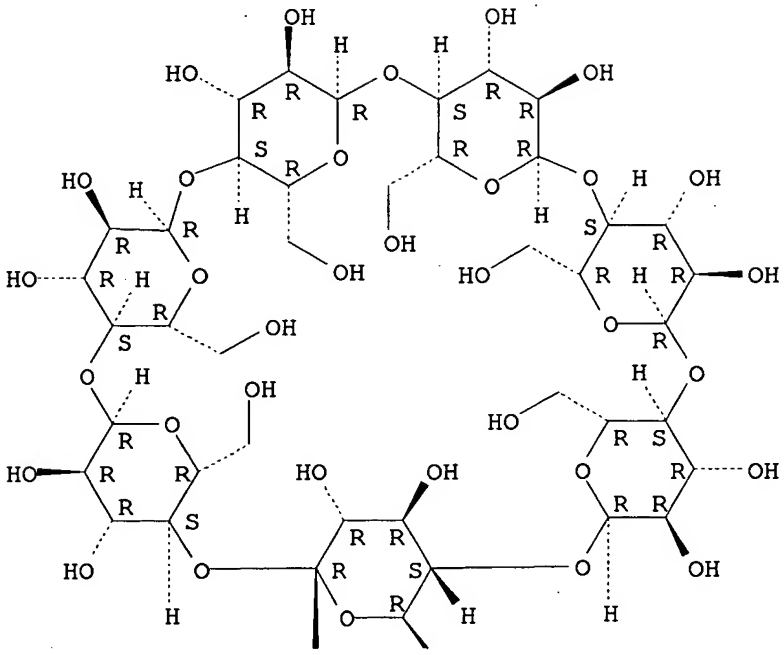


CM 2

CRN 7585-39-9
CMF C42 H70 O35

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A

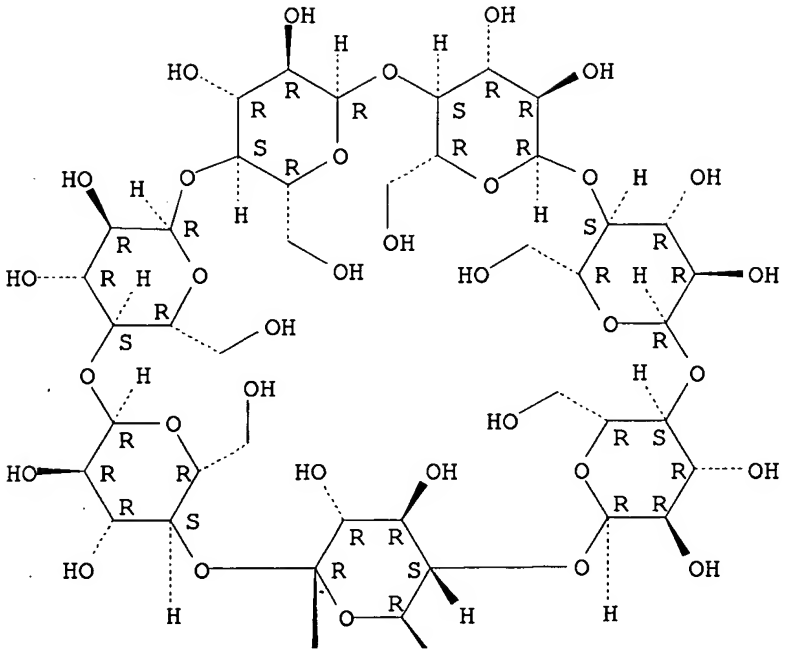
RN 845959-52-6 CAPLUS
CN β-Cyclodextrin, compd. with [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium methanesulfonate (1:1) (9CI) (CA INDEX NAME)

CM 1

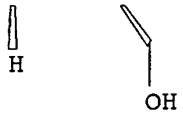
CRN 7585-39-9
CMF C42 H70 O35

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A

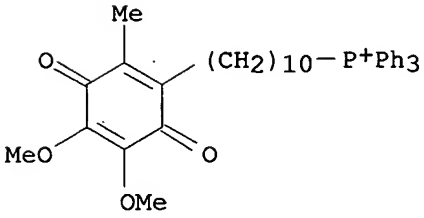


CM 2

CRN 845959-50-4
CMF C37 H44 O4 P . C H3 O3 S

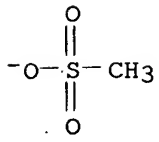
CM 3

CRN 444890-41-9
CMF C37 H44 O4 P

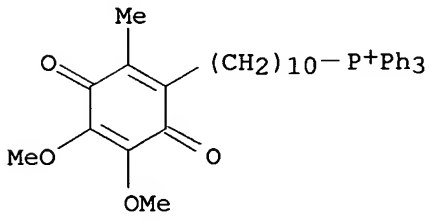


CM 4

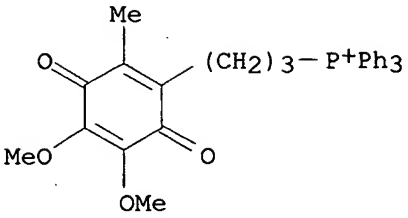
CRN 16053-58-0
CMF C H3 O3 S



IT 336184-91-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(mitoquinone derivative preparation for mitochondrially targeted antioxidant)
RN 336184-91-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



IT 845959-57-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(mitoquinone derivative preparation for mitochondrially targeted antioxidant)
RN 845959-57-1 CAPLUS
CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl-, bromide (1:1) (CA INDEX NAME)




● $Br^-$

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 22 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:710408 CAPLUS
DOCUMENT NUMBER: 141:236523
TITLE: Supplementation of Endothelial Cells with Mitochondria-targeted Antioxidants Inhibit Peroxide-induced Mitochondrial Iron Uptake, Oxidative Damage, and Apoptosis
AUTHOR(S): Dhanasekaran, Anuradha; Kotamraju, Srigiridhar; Kalivendi, Shasi V.; Matsunaga, Toshiyuki; Shang, Tiesong; Keszler, Agnes; Joseph, Joy; Kalyanaraman, B.
CORPORATE SOURCE: Department of Biophysics and Free Radical Research Center, Medical College of Wisconsin, Milwaukee, WI, 53226, USA
SOURCE: Journal of Biological Chemistry (2004), 279(36), 37575-37587
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

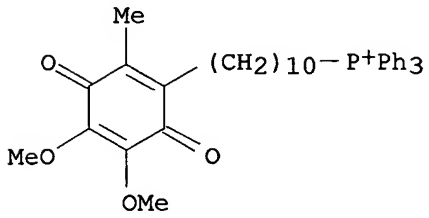
AB The mitochondria-targeted drugs mitoquinone (Mito-Q) and mitovitamin E (MitoVit-E) are a new class of antioxidants containing the triphenylphosphonium cation moiety that facilitates drug accumulation in mitochondria. In this study, Mito-Q (ubiquinone attached to a triphenylphosphonium cation) and MitoVit-E (vitamin E attached to a triphenylphosphonium cation) were used. The aim of this study was to test the hypothesis that mitochondria-targeted antioxidants inhibit peroxide-induced oxidative stress and apoptosis in bovine aortic endothelial cells (BAEC) through enhanced scavenging of mitochondrial reactive oxygen species, thereby blocking reactive oxygen species-induced transferrin receptor (TfR)-mediated iron uptake into mitochondria. Glucose/glucose oxidase-induced oxidative stress in BAECs was monitored by oxidation of dichlorodihydrofluorescein that was catalyzed by both intracellular H2O2 and transferrin iron transported into cells. Pretreatment of BAECs with Mito-Q (1 μM) and MitoVit-E (1 μM) but not untargeted antioxidants (e.g. vitamin E) significantly abrogated H2O2- and lipid peroxide-induced 2',7'-dichlorofluorescein fluorescence and protein oxidation Mitochondria-targeted antioxidants inhibit cytochrome c release, caspase-3 activation, and DNA fragmentation. Mito-Q and MitoVit-E inhibited H2O2- and lipid peroxide-induced inactivation of

complex I and aconitase, TfR overexpression, and mitochondrial uptake of 55Fe, while restoring the mitochondrial membrane potential and proteasomal activity. The authors conclude that Mito-Q or MitoVit-E supplementation of endothelial cells mitigates peroxide-mediated oxidant stress and maintains proteasomal function, resulting in the overall inhibition of TfR-dependent iron uptake and apoptosis.

IT 336184-91-9
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(supplementation of endothelial cells with mitochondria-targeted antioxidants inhibit peroxide-induced mitochondrial iron uptake, oxidative damage, and apoptosis)

RN 336184-91-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)




● $Br^-$

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

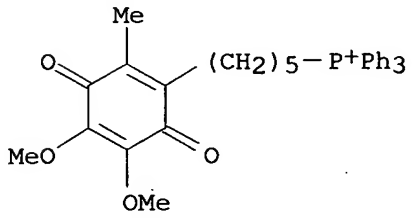
L4 ANSWER 23 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:601038 CAPLUS
DOCUMENT NUMBER: 141:290668
TITLE: Fine-tuning the hydrophobicity of a mitochondria-targeted antioxidant
AUTHOR(S): Asin-Cayuela, Jordi; Manas, Abdul-Rahman B.; James, Andrew M.; Smith, Robin A. J.; Murphy, Michael P.
CORPORATE SOURCE: Wellcome Trust/MRC Building, Medical Research Council Dunn Human Nutrition Unit, Cambridge, CB2 2XY, UK
SOURCE: FEBS Letters (2004), 571(1-3), 9-16
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:290668

AB The mitochondria-targeted antioxidant MitoQ comprises a ubiquinol moiety covalently attached through an aliphatic carbon chain to the lipophilic triphenylphosphonium cation. This cation drives the membrane potential-dependent accumulation of MitoQ into mitochondria, enabling the ubiquinol antioxidant to prevent mitochondrial oxidative damage far more effectively than untargeted antioxidants. We sought to fine-tune the hydrophobicity of MitoQ so as to control the extent of its membrane binding and penetration into the phospholipid bilayer, and thereby regulate its partitioning between the membrane and aqueous phases within

mitochondria and cells. To do this, MitoQ variants with 3, 5, 10 and 15 carbon aliphatic chains were synthesized. These mols. had a wide range of hydrophobicities with octan-1-ol/phosphate buffered saline partition coeffs. from 2.8 to 20,000. All MitoQ variants were accumulated into mitochondria driven by the membrane potential, but their binding to phospholipid bilayers varied from negligible for MitoQ3 to essentially total for MitoQ15. Despite the span of hydrophobicities, all MitoQ variants were effective antioxidants. Therefore, it is possible to fine-tune the degree of membrane association of MitoQ and other mitochondria targeted compds., without losing antioxidant efficacy. This indicates how the uptake and distribution of mitochondria-targeted compds. within mitochondria and cells can be controlled, thereby facilitating investigations of mitochondrial oxidative damage.

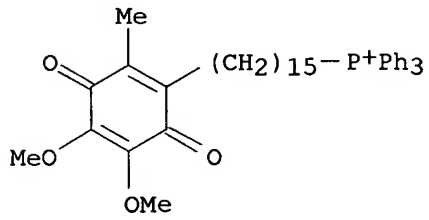
IT 764723-90-2P 764723-92-4P 845959-57-1P
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of MitoQ variants for fine-tuning the hydrophobicity of a mitochondria-targeted antioxidant)

RN 764723-90-2 CAPLUS
CN Phosphonium, [5-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentyl]triphenyl-, iodide (1:1) (CA INDEX NAME)




● $I^-$

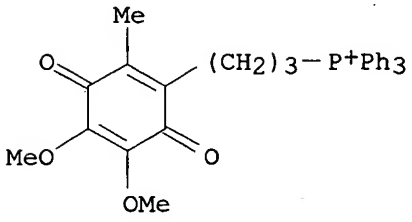
RN 764723-92-4 CAPLUS
CN Phosphonium, [15-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)pentadecyl]triphenyl-, bromide (1:1) (CA INDEX NAME)




● $Br^-$

RN 845959-57-1 CAPLUS
CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-

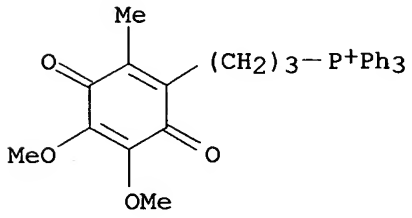
yl)propyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



IT 845959-58-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of MitoQ variants for fine-tuning the hydrophobicity of a mitochondria-targeted antioxidant)
RN 845959-58-2 CAPLUS
CN Phosphonium, [3-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)propyl]triphenyl-, methanesulfonate (1:1) (CA INDEX NAME)

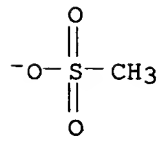
CM 1

CRN 794485-93-1
CMF C30 H30 O4 P



CM 2

CRN 16053-58-0
CMF C H3 O3 S

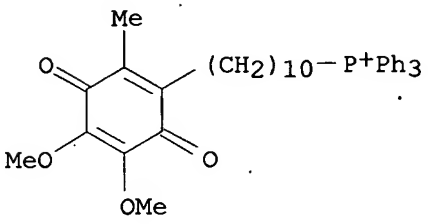


REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:434607 CAPLUS
DOCUMENT NUMBER: 141:49659
TITLE: Mitochondria-derived reactive oxygen species mediate blue light-induced death of retinal pigment epithelial cells
AUTHOR(S): King, Ayala; Gottlieb, Eyal; Brooks, David G.; Murphy, Michael P.; Dunaief, Joshua L.
CORPORATE SOURCE: F.M. Kirby Center for Molecular Ophthalmology, Scheie Eye Institute, University of Pennsylvania, Philadelphia, PA, USA
SOURCE: Photochemistry and Photobiology (2004), 79(5), 470-475
CODEN: PHCBAP; ISSN: 0031-8655
PUBLISHER: American Society for Photobiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Throughout the lifetime of an individual, light is focused onto the retina. The resulting photooxidative stress can cause acute or chronic retinal damage. The pathogenesis of age-related macular degeneration (AMD), the leading cause of legal blindness in the developed world, involves oxidative stress and death of the retinal pigment epithelium (RPE) followed by death of the overlying photoreceptors. Evidence suggests that damage due to exposure to light plays a role in AMD and other age-related eye diseases. In this work a system for light-induced damage and death of the RPE, based on the human ARPE-19 cell line, was used. Induction of mitochondria-derived reactive oxygen species (ROS) is shown to play a critical role in the death of cells exposed to short-wavelength blue light (425 ± 20 nm). ROS and cell death are blocked either by inhibiting the mitochondrial electron transport chain or by mitochondria-specific antioxidants. These results show that mitochondria are an important source of toxic oxygen radicals in blue light-exposed RPE cells and may indicate new approaches for treating AMD using mitochondria-targeted antioxidants.

IT 336184-91-9
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mitochondria-derived ROS mediate blue light-induced death of retinal pigment epithelium)
RN 336184-91-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)



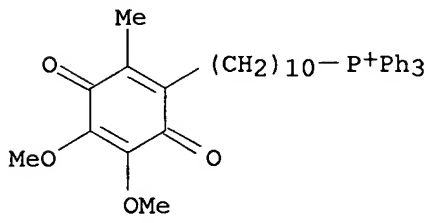

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 25 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:826167 CAPLUS
DOCUMENT NUMBER: 140:53354
TITLE: Mitochondria-targeted antioxidants protect Friedreich Ataxia fibroblasts from endogenous oxidative stress more effectively than untargeted antioxidants
AUTHOR(S): Jauslin, Matthias L.; Meier, Thomas; Smith, Robin A. J.; Murphy, Michael P.
CORPORATE SOURCE: MyoContract Ltd., Liestal, CH-4410, Switz.
SOURCE: FASEB Journal (2003), 17(13), 1972-1974, 10.1096/fj.03-0240fje
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Friedreich Ataxia (FRDA), the most common inherited ataxia, arises from defective expression of the mitochondrial protein frataxin, which leads to increased mitochondrial oxidative damage. Therefore, antioxidants targeted to mitochondria should be particularly effective at slowing disease progression. To test this hypothesis, we compared the efficacy of mitochondria-targeted and untargeted antioxidants derived from coenzyme Q10 and from vitamin E at preventing cell death due to endogenous oxidative stress in cultured fibroblasts from FRDA patients in which glutathione synthesis was blocked. The mitochondria-targeted antioxidant MitoQ was several hundredfold more potent than the untargeted analog idebenone. The mitochondria-targeted antioxidant MitoVit E was 350-fold more potent than the water soluble analog Trolox. This is the first demonstration that mitochondria-targeted antioxidants prevent cell death that arises in response to endogenous oxidative damage. Targeted antioxidants may have therapeutic potential in FRDA and in other disorders involving mitochondrial oxidative damage.

IT 444890-41-9
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mitochondria-targeted antioxidants protect Friedreich Ataxia fibroblasts from endogenous oxidative stress more effectively than untargeted antioxidants)

RN 444890-41-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)




REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

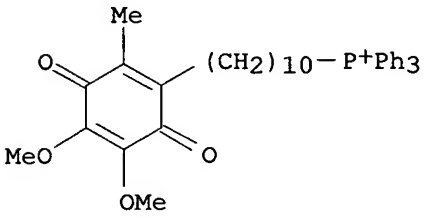
L4 ANSWER 26 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:426934 CAPLUS
DOCUMENT NUMBER: 140:74526
TITLE: MitoQ counteracts telomere shortening and elongates lifespan of fibroblasts under mild oxidative stress
AUTHOR(S): Saretzki, Gabriele; Murphy, Michael P.; von Zglinicki, Thomas
CORPORATE SOURCE: Gerontology, Institute of Aging and Health, Newcastle University, Newcastle upon Tyne, NE4 6BE, UK
SOURCE: Aging Cell (2003), 2(2), 141-143
CODEN: ACGECQ; ISSN: 1474-9718
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of the mitochondria-specific antioxidant mitoQ [10-(6'-ubiquinonyl) decyltriphenylphosphonium bromide] in human fibroblasts under mild stress conditions was investigated. Treatment of MRC-5 fibroblasts with mitoQ under these conditions significantly decreased the cellular peroxide content and elongated the replicative lifespan. MitoQ treatment completely prevented the rise in telomere shortening rate due to hyperoxia and instead gave a negligible rate of telomere shortening.

IT 336184-91-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(MitoQ counteracts telomere shortening and elongates lifespan of human fibroblasts under mild oxidative stress)

RN 336184-91-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)




● $Br^-$

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

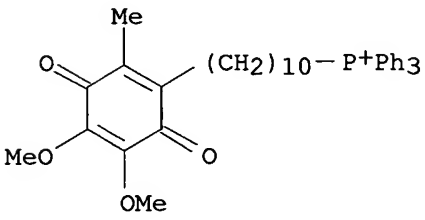
L4 ANSWER 27 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:411988 CAPLUS
DOCUMENT NUMBER: 137:139797
TITLE: Prevention of mitochondrial oxidative damage using targeted antioxidants
AUTHOR(S): Kelso, Geoffrey F.; Porteous, Carolyn M.; Hughes, Gillian; Ledgerwood, Elizabeth C.; Gane, Alison M.; Smith, Robin A. J.; Murphy, Michael P.
CORPORATE SOURCE: Departments of Chemistry, University of Otago, Dunedin, N. Z.
SOURCE: Annals of the New York Academy of Sciences (2002),

959(Increasing Health Life Span), 263-274
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Two mitochondria-targeted antioxidants that can selectively block mitochondrial oxidative damage and prevent some types of cell death were developed. They were ubiquinone and tocopherol derivs. targeted to mitochondria by covalent attachment to the lipophilic triphenylphosphonium cation. The effects of the 2 derivs. and nontargeted ubiquinone and tocopherol were examined in vitro in rat liver and beef heart mitochondrial prepns. and in Jurkat human T lymphocyte cell line and in vivo in female Swiss Webster mice. Because of the large mitochondrial membrane potential, these cations can accumulated within mitochondria inside the cells, where the antioxidant moiety prevented lipid peroxidn. and protected the mitochondria from oxidative damage. The mitochondrially localized ubiquinone derivative also protected mammalian cells from hydrogen peroxide-induced apoptosis while the nontargeted ubiquinone analog was ineffective against cell apoptosis. When fed to mice, the 2 derivs. accumulated in the brain, heart, and liver. These mitochondria-targeted antioxidants may help in investigations of the role of mitochondrial oxidative damage in animal models of aging.

IT 444890-41-9
RL: BSU (Biological study, unclassified); FFD (Food or feed use); BIOL (Biological study); USES (Uses)
(dietary ubiquinone and tocopherol targeted antioxidant derivs. use in prevention of mitochondrial oxidative damage in vitro and in mice)

RN 444890-41-9 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl- (CA INDEX NAME)




REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 28 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:137933 CAPLUS
DOCUMENT NUMBER: 134:322127
TITLE: Selective targeting of a redox-active ubiquinone to mitochondria within cells. Antioxidant and antiapoptotic properties
AUTHOR(S): Kelso, Geoffrey F.; Porteous, Carolyn M.; Coulter, Carolyn V.; Hughes, Gillian; Porteous, William K.; Ledgerwood, Elizabeth C.; Smith, Robin A. J.; Murphy, Michael P.
CORPORATE SOURCE: Department of Chemistry, University of Otago, Dunedin, N. Z.

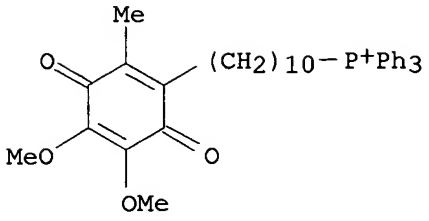
SOURCE: Journal of Biological Chemistry (2001), 276(7), 4588-4596
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:322127

AB With the recognition of the central role of mitochondria in apoptosis, there is a need to develop specific tools to manipulate mitochondrial function within cells. Here we report on the development of a novel antioxidant that selectively blocks mitochondrial oxidative damage, enabling the roles of mitochondrial oxidative stress in different types of cell death to be inferred. This antioxidant, named mitoQ, is a ubiquinone derivative targeted to mitochondria by covalent attachment to a lipophilic triphenylphosphonium cation through an aliphatic carbon chain. Due to the large mitochondrial membrane potential, the cation was accumulated within mitochondria inside cells, where the ubiquinone moiety inserted into the lipid bilayer and was reduced by the respiratory chain. The ubiquinol derivative thus formed was an effective antioxidant that prevented lipid peroxidn. and protected mitochondria from oxidative damage. After detoxifying the reactive oxygen species peroxynitrite, the ubiquinol moiety was regenerated by the respiratory chain enabling its antioxidant activity to be recycled. In cell culture studies, the mitochondrially localized antioxidant protected mammalian cells from hydrogen peroxide-induced apoptosis but not from apoptosis induced by staurosporine or tumor necrosis factor-α. This was compared with untargeted ubiquinone analogs, which were ineffective in preventing apoptosis. These results suggest that mitochondrial oxidative stress may be a critical step in apoptosis induced by hydrogen peroxide but not for apoptosis induced by staurosporine or tumor necrosis factor-α. We have shown that selectively manipulating mitochondrial antioxidant status with targeted and recyclable antioxidants is a feasible approach to investigate the role of mitochondrial oxidative damage in apoptotic cell death. This approach will have further applications in investigating mitochondrial dysfunction in a range of exptl. models.

IT 336184-91-9P 336184-92-0P
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(novel redox-active ubiquinone mitoQ displays antioxidant and antiapoptotic properties in mitochondria)

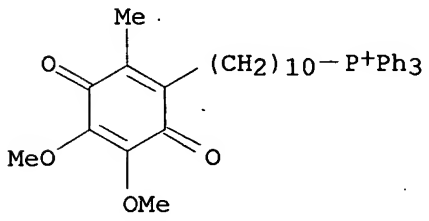
RN 336184-91-9 CAPLUS

CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide (1:1) (CA INDEX NAME)




● $Br^-$

RN 336184-92-0 CAPLUS
CN Phosphonium, [10-(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenyl-, bromide, labeled with tritium (9CI) (CA INDEX NAME)




● $Br^-$

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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---Logging off of STN---

END

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Executing the logoff script...

ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:LOG Y

LOGOFF? (Y)/N/HOLD:
'LOG Y' IS NOT VALID HERE
For an explanation, enter "HELP LOGOFF".

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---Logging off of STN---

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Executing the logoff script...

=> LOG Y

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